Harris, A.
09/766944

FILE 'REGISTRY' ENTERED AT 14:26:09 ON 23 FEB 2005
E "C3 EXOENZYME"/CN 5
L1 1 S E3

FILE 'CAPLUS' ENTERED AT 14:26:33 ON 23 FEB 2005
L2 1700 S L1 OR C3(W)(EXOENZYME OR EXO ENZYME)
L3 5 S L2 AND P27

L3 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 08 Apr 2004
ACCESSION NUMBER: 2004:287758 CAPLUS
DOCUMENT NUMBER: 140:302345
TITLE: Genes showing altered patterns of expression in the central nervous system in multiple sclerosis and their diagnostic and therapeutic use
INVENTOR(S): Dangond, Fernando; Hwang, Daehee; Gullans, Steven R.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004028339	A2	20040408	WO 2003-US29451	20030925
WO 2004028339	A3	20040805		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004156826	A1	20040812	US 2003-670766	20030925
PRIORITY APPLN. INFO.:			US 2002-414219P P	20020927

AB The present invention identifies a number of gene markers whose expression is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression.

IT **58319-92-9**, ADP-ribosyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for, in treatment of multiple sclerosis; genes showing altered patterns of expression in central nervous system in multiple sclerosis and their diagnostic and therapeutic use)

L3 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 17 Jan 2003
ACCESSION NUMBER: 2003:43009 CAPLUS
DOCUMENT NUMBER: 138:66676

TITLE: **P27** prevents cellular migration
INVENTOR(S): Marks, Andrew R.; Marx, Steven O.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U. S. Ser. No. 766,944.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003013638	A1	20030116	US 2002-172027	20020614
US 2002098998	A1	20020725	US 2001-766944	20010122
WO 2003106970	A2	20031224	WO 2003-US18970	20030612
WO 2003106970	A3	20040910		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-766944 A2 20010122
US 2002-172027 A 20020614

AB This invention provides methods of preventing cellular migration and of treating cardiovascular diseases and tumor metastasis by increasing the intracellular concentration of cyclin-dependent kinase inhibitor **p27** or **C3 exoenzyme** or by decreasing the intracellular concentration of Rho-kinase, and methods of identifying chemical compds. for use in such treatments.

IT **58319-92-9, c3 Exoenzyme**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclin-dependent kinase inhibitor **p27** prevents cellular migration)

L3 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 26 Jul 2002
ACCESSION NUMBER: 2002:556098 CAPLUS
DOCUMENT NUMBER: 137:103877
TITLE: **P27** prevents cellular migration, methods for treatment of cardiovascular diseases and tumor metastases, and compound identification method
INVENTOR(S): Marks, Andrew R.; Marx, Steven O.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002098998	A1	20020725	US 2001-766944	20010122
CA 2434696	AA	20020725	CA 2002-2434696	20020122
WO 2002056753	A2	20020725	WO 2002-US1961	20020122
WO 2002056753	A3	20030403		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1359904	A2	20031112	EP 2002-707550	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517880	T2	20040617	JP 2002-557267	20020122
US 2003013638	A1	20030116	US 2002-172027	20020614
PRIORITY APPLN. INFO.:			US 2001-766944 A	20010122
			WO 2002-US1961 W	20020122

AB The invention provides methods for preventing cellular migration and for treating cardiovascular diseases and tumor metastasis by increasing cyclin-dependent kinase inhibitor **p27** activity, as well as methods for identifying chemical compds. for use in such treatments.

IT **58319-92-9, C3 Exoenzyme**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(**P27** prevents cellular migration, methods for treatment of cardiovascular diseases and tumor metastases, and compound identification method)

L3 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 19 May 2002
ACCESSION NUMBER: 2002:371215 CAPLUS
DOCUMENT NUMBER: 137:91252
TITLE: Rho activity can alter the translation of **p27** mRNA and is important for RasV12-induced transformation in a manner dependent on **p27** status
AUTHOR(S): Vidal, Anxo; Millard, S. Sean; Miller, Jeffrey P.; Koff, Andrew
CORPORATE SOURCE: Programs in Molecular Biology, Memorial Sloan Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Journal of Biological Chemistry (2002), 277(19), 16433-16440
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The amount of p27Kip1 establishes a threshold to which G1 cyclin-cyclin-dependent kinase complexes must surpass prior to cells

progressing into S-phase. The amount of **p27** is greatest in G0 cells, intermediate in G1 cells, and lowest in S-phase cells. However, there is little known regarding the pathways and mechanisms controlling **p27** accumulation in G0 cells. We report that inhibition of Rho, by either lovastatin or **C3 exoenzyme**, can increase the translational efficiency of **p27** mRNA. Similar pharmacol. inhibition of the phosphatidylinositol 3-kinase, the S6 kinase, and the Mek1 kinase pathways all fail to increase translational efficiency in MDA468 cells. This Rho-responsive element lies within a 300-nucleotide region at the 3'-end of the mRNA. By supporting the significance of this signaling pathway to Rho function, we showed that the suppression of RasV12 transformation by RhoAN19 is blocked in **p27**-/- cells. In contrast this activity is not blocked in Rb-/- or p16-/- cells. The resistance of **p27**-/- cells to RhoAN19 is not associated with a failure of RhoAN19 to accumulate to amts. sufficient to block Rho activity as measured by the organization of actin stress fibers. Together these results indicate a link between Rho and **p27**.

IT **58319-92-9, C3 Exoenzyme**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Rho activity can alter the translation of **p27** mRNA and is important for RasV12-induced transformation in a manner dependent on **p27** status)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 17 Jan 1997
ACCESSION NUMBER: 1997:34374 CAPLUS
DOCUMENT NUMBER: 126:129768
TITLE: Geranylgeranylated Rho small GTPase(s) are essential for the degradation of p27Kip1 and facilitate the progression from G1 to S phase in growth-stimulated rat FRTL-5 cells
AUTHOR(S): Hirai, Aizan; Nakamura, Susumu; Noguchi, Yoshihiko; Yasuda, Tatsuji; Kitagawa, Masatoshi; Tatsuno, Ichiro; Oeda, Toru; Tahara, Kazuo; Terano, Takashi; Narumiya, Shuh; Kohn, Leonard D.; Saito, Yasushi
CORPORATE SOURCE: Second Dep. Internal Med., Chiba Univ. Med. Sch., Chiba, 260, Japan
SOURCE: Journal of Biological Chemistry (1997), 272(1), 13-16
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclin-dependent kinase (Cdk) enzymes are activated for entry into the S phase of the cell cycle. Elimination of Cdk inhibitor protein p27Kip1 during the G1 to S phase is required for the activation process. An inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase prevents its elimination and leads to G1 arrest. Mevalonate and its metabolite, geranylgeranyl pyrophosphate, but not farnesyl pyrophosphate, restore the inhibitory effect of pravastatin on the degradation of **p27** and allow Cdk2 activation. By the addition of geranylgeranyl pyrophosphate, Rho small GTPase(s) are geranylgeranylated and translocated to membranes during G1/S progression. The restoring effect of geranylgeranyl pyrophosphate is abolished with botulinum **C3 exoenzyme**, which

specifically inactivates Rho. These results indicate (i) among mevalonate metabolites, geranylgeranyl pyrophosphate is absolutely required for the elimination of **p27** followed by Cdk2 activation; (ii) geranylgeranylated Rho small GTPase(s) promote the degradation of **p27** during G1/S transition in FRTL-5 cells.

IT **58319-92-9, C3 Exoenzyme**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(geranylgeranylated Rho small GTPase(s) are essential for degradation of p27Kip1 and facilitate progression from G1 to S phase in growth-stimulated rat FRTL-5 cells in relation to)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 2086 SEA ABB=ON PLU=ON C3(W)(BOTULIN? OR TRANSFERASE) OR (EXOENZYME OR EXO ENZYME)(W)(C3 OR S OR T OR U) OR HALOVIBRIN OR (ADENOSINE OR ADP)(3W)((RIBOSE OR RIBOSYL OR RIBO)(W)TRANSFERASE OR RIBOSYLTRANSFERASE OR RIBOTRANSFERASE)
L5 3 SEA ABB=ON PLU=ON L4 AND P27
L6 2 SEA ABB=ON PLU=ON L5 NOT L3

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 24 Sep 2004
ACCESSION NUMBER: 2004:780908 CAPLUS
DOCUMENT NUMBER: 141:295286
TITLE: Biomarker identification for evaluating caloric restricted diet program in mammals
INVENTOR(S): Spindler, Stephen R.; Dhahbi, Joseph M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004081537	A2	20040923	WO 2004-US7737		20040312
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004180003	A1	20040916	US 2003-387743		20030312
US 2004191775	A1	20040930	US 2003-387786		20030312
US 2005013776	A1	20050120	US 2003-622160		20030716
PRIORITY APPLN. INFO.:			US 2003-387743	A	20030312
			US 2003-387786	A	20030312
			US 2003-622160	A	20030716

AB Methods of identifying biomarkers of calorie restriction and of examining the dynamics of calorie restriction are presented. In addition, the invention provides methods of selecting mimetics of calorie restriction.

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 06 Oct 1999
ACCESSION NUMBER: 1999:631925 CAPLUS
DOCUMENT NUMBER: 131:320723
TITLE: Regulation of the hepatocyte cell cycle by type I collagen matrix: role of cyclin D1
AUTHOR(S): Hansen, Linda K.; Albrecht, Jeffrey H.
CORPORATE SOURCE: Department of Laboratory Medicine and Pathology, and Cancer Center, University of Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Journal of Cell Science (1999), 112(17), 2971-2981
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rat hepatocytes adherent to a rigid film of type I collagen will spread and enter S phase, while those attached to collagen gel or a dried collagen substrate remain round and quiescent. The current studies were initiated to determine the mechanism by which these different substrates differentially influence cell cycle progression. Cyclin D1 mRNA and protein expression and associated kinase activity was low on dried collagen relative to collagen film. In contrast, cyclin E and cdk2 protein levels were similar on the two substrates. Although cyclin E and cdk2 were present, cells on dried collagen lacked cdk2 kinase activity. **P27** protein levels did not differ between dried collagen and film, but more **p27** was associated with cdk2 in cells on dried collagen than those on collagen film. Cyclin D1 expression on collagen film was inhibited by cytochalasin D and **exoenzyme C3**, suggesting a role for the GTP-binding protein, Rho, in regulating cyclin D1 expression. Cyclin D1 over-expression induced hepatocytes into S phase in the absence of cell shape change on dried collagen or collagen gel. These results demonstrate a novel, substrate-dependent mechanism for cyclin D1 expression in hepatocytes, and also demonstrate that cyclin D1 overexpression allows shape-independent S phase entry.
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:32:07 ON 23 FEB 2005)
L7 82 SEA ABB=ON PLU=ON L3 OR L5
L8 46 DUP REM L7 (36 DUPLICATES REMOVED)
L9 38 SEA ABB=ON PLU=ON L8 AND ((CARDIAC OR CARDIOVASCULAR OR CARDIO VASCULAR OR HEART)(S)(DISEAS? OR DISORDER) OR ATHEROSCLER? OR ARTERIOPATH? OR RESTENOSIS OR RESTENOT? OR METASTAS? OR METASTAT? OR CANCER? OR CARCIN? OR TUMOUR OR TUMOR OR NEOPLAS?)

L9 ANSWER 1 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2002273321 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11875067
TITLE: Rho activity can alter the translation of **p27** mRNA and is important for RasV12-induced transformation in

a manner dependent on **p27** status.

AUTHOR: Vidal Anxo; Millard S Sean; Miller Jeffrey P; Koff Andrew
CORPORATE SOURCE: Programs in Molecular Biology, Memorial Sloan Kettering Cancer Center, New York, New York 10021, USA.
CONTRACT NUMBER: CA08748 (NCI)
GM52597 (NIGMS)
SOURCE: Journal of biological chemistry, (2002 May 10) 277 (19) 16433-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20030105
Entered Medline: 20020613

AB The amount of **p27**(Kip1) establishes a threshold to which G(1) cyclin-cyclin-dependent kinase complexes must surpass prior to cells progressing into S-phase. The amount of **p27** is greatest in G(0) cells, intermediate in G(1) cells, and lowest in S-phase cells. However, there is little known regarding the pathways and mechanisms controlling **p27** accumulation in G(0) cells. We report that inhibition of Rho, by either lovastatin or **C3 exoenzyme**, can increase the translational efficiency of **p27** mRNA. Similar pharmacologic inhibition of the phosphatidylinositol 3-kinase, the S6 kinase, and the Mek1 kinase pathways all fail to increase translational efficiency in MDA468 cells. This Rho-responsive element lies within a 300-nucleotide region at the 3'-end of the mRNA. By supporting the significance of this signaling pathway to Rho function, we showed that the suppression of Ras(V12) transformation by RhoA(N19) is blocked in **p27**-/- cells. In contrast this activity is not blocked in Rb-/- or p16-/- cells. The resistance of **p27**-/- cells to RhoA(N19) is not associated with a failure of RhoA(N19) to accumulate to amounts sufficient to block Rho activity as measured by the organization of actin stress fibers. Together these results indicate a link between Rho and **p27**.

L9 ANSWER 2 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2001349617 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11413088
TITLE: Role for **p27**(Kip1) in Vascular Smooth Muscle Cell Migration.
COMMENT: Comment in: Circulation. 2001 Jun 19;103(24):2879-81.
PubMed ID: 11413073
AUTHOR: Sun J; Marx S O; Chen H J; Poon M; Marks A R; Rabbani L E
CORPORATE SOURCE: Cardiology Division, Center for Molecular Cardiology, Department of Medicine, Columbia University College of Physicians and Surgeons, Mount Sinai School of Medicine, New York, NY, USA.
CONTRACT NUMBER: R03-TW-00949 (FIC)
R01-AI-39794 (NIAID)
R01-HL-30290 (NHLBI)
R01-HL-56180 (NHLBI)
SOURCE: Circulation, (2001 Jun 19) 103 (24) 2967-72.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB BACKGROUND: Rapamycin is a potent inhibitor of smooth muscle cell (SMC) proliferation and migration. Rapamycin-mediated inhibition of SMC proliferation is associated with upregulation of the cyclin-dependent kinase inhibitor **p27**(Kip1). Previously, we showed that mixed embryonic fibroblasts obtained from **p27**(Kip1)(-/-) mice were relatively rapamycin-resistant, suggesting that **p27**(Kip1) plays an integral role in modulating the antiproliferative effects of rapamycin. We hypothesized that the antimigratory effect of rapamycin may also be mediated by **p27**(Kip1). METHODS AND RESULTS: Rapamycin (1 to 10 nmol/L) inhibited basic fibroblast growth factor-induced migration of wild-type (WT) but not **p27**(Kip1)(-/-) SMCs in a dose-dependent manner ($P<0.05$) in a modified Boyden chamber. The effects of rapamycin on aortic SMC explant migration were also studied with WT, **p27**(+/-), and **p27**(-/-) mice. Rapamycin 4 mg. kg(-1). d(-1) IP for 5 days inhibited SMC migration by 90% in the WT and **p27**(Kip1)(+/-) ($P<0.05$) but not **p27**(Kip1)(-/-) animals. CONCLUSIONS: Lack of **p27**(Kip1) reduces rapamycin-mediated inhibition of SMC migration. These novel findings suggest a role for **p27**(Kip1) in the signaling pathway(s) that regulates SMC migration.

L9 ANSWER 3 OF 38 MEDLINE on STN
ACCESSION NUMBER: 1999404789 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10477139
TITLE: Short-term pravastatin mediates growth inhibition and apoptosis, independently of Ras, via the signaling proteins p27Kip1 and P13 kinase.
AUTHOR: Weiss R H; Ramirez A; Joo A
CORPORATE SOURCE: Department of Internal Medicine, University of California, Davis 95616, USA.. rhweiss@ucdavis.edu
SOURCE: Journal of the American Society of Nephrology : JASN, (1999 Sep) 10 (9) 1880-90.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991104

AB Growth factor-stimulated DNA synthesis in a variety of cell lines has been shown to be decreased after overnight (or longer) treatment with the 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, the statins. Although this anti-mitogenic effect had been presumed to be the result of the impairment of Ras lipidation, a stable modification (T1/2 approximately 20 h), this study provides new data demonstrating that brief (approximately 1 h) pretreatment of rat vascular smooth muscle cells with 100 microM pravastatin before platelet-derived growth factor-BB (PDGF-BB)

stimulation results in attenuation of DNA synthesis through a Ras-independent mechanism. PDGF-BB-stimulated PDGF-beta receptor tyrosine phosphorylation, Ras activity, and mitogen-activated protein/extracellular signal-regulated kinase activity are unaffected by from 10 min to 1 h of pravastatin incubation, while Raf activity is markedly increased after 1 h of pravastatin. Phosphatidylinositol-3 kinase activity and phosphorylation of its downstream effector Akt are decreased after 1 h pravastatin incubation. Rho is stabilized by pravastatin, and ADP-ribosylation of Rho by **C3 exoenzyme** decreases PDGF-stimulated phosphatidylinositol-3 kinase activity, mimicking the effect of pravastatin on this signaling protein. Levels of the cyclin-dependent kinase inhibitor p27Kip1 are increased when cells were preincubated with pravastatin for 1 h and then exposed to PDGF, and apoptosis is induced by pravastatin incubation times as short as 1 to 4 h. Thus, short-term, high-dose pravastatin inhibits vascular smooth muscle cell growth and induces apoptosis independently of Ras, likely by means of the drug's effect on p27Kip1, mediated by Rho and/or phosphatidylinositol-3 kinase. This work demonstrates for the first time that the statins may be therapeutically useful when applied for short periods of time such that potential toxicity of long-term statin use (such as chronic Ras inhibition) may be avoided, suggesting future therapeutic directions for statin research.

L9 ANSWER 4 OF 38 MEDLINE on STN
ACCESSION NUMBER: 1999375345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10444391
TITLE: Regulation of the hepatocyte cell cycle by type I collagen matrix: role of cyclin D1.
AUTHOR: Hansen L K; Albrecht J H
CORPORATE SOURCE: Department of Laboratory Medicine and Pathology, and Cancer Center, University of Minnesota, Minneapolis, MN 55455, USA.. hanse066@tc.umn.edu
CONTRACT NUMBER: 1R01-DK-54921 (NIDDK)
SOURCE: Journal of cell science, (1999 Sep) 112 (Pt 17) 2971-81. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991229

AB Rat hepatocytes adherent to a rigid film of type I collagen will spread and enter S phase, while those attached to collagen gel or a dried collagen substrate remain round and quiescent. The current studies were initiated to determine the mechanism by which these different substrates differentially influence cell cycle progression. Cyclin D1 mRNA and protein expression and associated kinase activity was low on dried collagen relative to collagen film. In contrast, cyclin E and cdk2 protein levels were similar on the two substrates. Although cyclin E and cdk2 were present, cells on dried collagen lacked cdk2 kinase activity. **p27** protein levels did not differ between dried collagen and film, but more **p27** was associated with cdk2 in cells on dried collagen than those on collagen film. Cyclin D1 expression on collagen film was inhibited by cytochalasin D and **exoenzyme C3**,

suggesting a role for the GTP-binding protein, Rho, in regulating cyclin D1 expression. Cyclin D1 over-expression induced hepatocytes into S phase in the absence of cell shape change on dried collagen or collagen gel. These results demonstrate a novel, substrate-dependent mechanism for cyclin D1 expression in hepatocytes, and also demonstrate that cyclin D1 over-expression allows shape-independent S phase entry.

L9 ANSWER 5 OF 38 MEDLINE on STN
ACCESSION NUMBER: 1999369904 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10440923
TITLE: Effect of cyclin E overexpression on lovastatin-induced G1 arrest and RhoA inactivation in NIH3T3 cells.
AUTHOR: Ghosh P M; Moyer M L; Mott G E; Kreisberg J I
CORPORATE SOURCE: Department of Pathology, University of Texas Health Science Center, San Antonio, Texas 78284, USA.
SOURCE: Journal of cellular biochemistry, (1999 Sep 15) 74 (4) 532-43.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 20000303
Entered Medline: 19991012

AB The HMG-CoA reductase inhibitor, lovastatin, blocks targeting of the Rho and Ras families of small GTPases to their active sites by inhibiting protein prenylation. Control NIH3T3 cells, and those overexpressing human cyclin E protein were treated with lovastatin for 24 h to determine the effects of cyclin E overexpression on lovastatin-induced growth arrest and cell rounding. Lovastatin treatment (10 microM) of control 3T3 cells resulted in growth arrest at G1 accompanied by actin stress fiber disassembly, cell rounding, and decreased active RhoA from the membranous protein fraction. By contrast, in NIH3T3 cells overexpressing cyclin E, lovastatin did not cause loss of RhoA from the membrane (active) protein fraction, actin stress fiber disassembly, cell rounding or growth arrest within 24 h. Analysis of cell cycle proteins showed that 24 h of lovastatin treatment in the control cells caused an elevation in the levels of the cyclin-dependent kinase inhibitor **p27**(kip1), inhibition of both cyclin E- and cyclin A-dependent kinase activity, and decreased levels of hyperphosphorylated retinoblastoma protein (pRb). By contrast, lovastatin treatment of the cyclin E overexpressors did not suppress either cyclin E- or cyclin A-dependent kinase activity, nor did it alter the level of maximally phosphorylated pRb, despite increased levels of **p27**(kip1). However, by 72 h, the cyclin E overexpressors rounded up but remained attached to the substratum, indicating a delayed response to lovastatin. In contrast with lovastatin, inactivation of membrane-bound Rho proteins (i.e., GTP-bound RhoA, RhoB, RhoC) with botulinum **C3 transferase** caused cell rounding and G1 growth arrest in both cell types but did not inhibit cyclin E-dependent histone kinase activity in the cyclin E overexpressors. In addition, 24 h of cycloheximide treatment caused depletion of RhoA from the membrane (active) fraction in neo cells, but in the cells overexpressing cyclin E, RhoA remained in the active (membrane-associated) fraction. Our observations suggest that (1) RhoA activation occurs

downstream of cyclin E-dependent kinase activation, and (2) overexpression of cyclin E decreased the turnover rate of active RhoA.

L9 ANSWER 6 OF 38 MEDLINE on STN
ACCESSION NUMBER: 1999348331 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10419514
TITLE: 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors attenuate vascular smooth muscle proliferation by preventing rho GTPase-induced down-regulation of **p27**(Kip1).
AUTHOR: Laufs U; Marra D; Node K; Liao J K
CORPORATE SOURCE: Cardiovascular Division, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachustts 02115, USA.
CONTRACT NUMBER: HL-52233 (NHLBI)
SOURCE: Journal of biological chemistry, (1999 Jul 30) 274 (31) 21926-31.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 20000303
Entered Medline: 19990819

AB The mechanism by which platelet-derived growth factor (PDGF) regulates vascular smooth muscle cell (SMC) DNA synthesis is unknown, but may involve isoprenoid intermediates of the cholesterol biosynthetic pathway. Inhibition of isoprenoid synthesis with the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor, simvastatin (Sim, 1-10 microM), inhibited PDGF-induced SMC DNA synthesis by >95%, retinoblastoma gene product hyperphosphorylation by 90%, and cyclin-dependent kinases (cdk)-2, -4, and -6 activity by 80 +/- 5, 50 +/- 3, and 48 +/- 3%, respectively. This correlated with a 20-fold increase in **p27**(Kip1) without changes in p16, p21(Waf1), or p53 levels compared with PDGF alone. Since Ras and Rho require isoprenoid modification for membrane localization and are implicated in cell cycle regulation, we investigated the effects of Sim on Ras and Rho. Up-regulation of **p27**(Kip1) and inhibition of Rho but not Ras membrane translocation by Sim were reversed by geranylgeranylpyrophosphate, but not farnesylpyrophosphate. Indeed, inhibition of Rho by Clostridium botulinum **C3 transferase** or overexpression of dominant-negative N19RhoA mutant increased **p27**(Kip1) and inhibited retinoblastoma hyperphosphorylation. In contrast, activation of Rho by Escherichia coli cytotoxic necrotizing factor-1 decreased **p27**(Kip1) and increased SMC DNA synthesis. These findings indicate that the down-regulation of **p27**(Kip1) by Rho GTPase mediates PDGF-induced SMC DNA synthesis and suggest a novel direct effect of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors on the vascular wall.

L9 ANSWER 7 OF 38 MEDLINE on STN
ACCESSION NUMBER: 1998070493 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9407076
TITLE: Ras-stimulated extracellular signal-related kinase 1 and RhoA activities coordinate platelet-derived growth

factor-induced G1 progression through the independent regulation of cyclin D1 and **p27**.
AUTHOR: Weber J D; Hu W; Jefcoat S C Jr; Raben D M; Baldassare J J
CORPORATE SOURCE: Department of Cell and Molecular Biology, St. Louis University, St. Louis, Missouri 63104, USA.
CONTRACT NUMBER: GM51593 (NIGMS)
HL40901 (NHLBI)
SOURCE: Journal of biological chemistry, (1997 Dec 26) 272 (52) 32966-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 20000303
Entered Medline: 19980123

AB Platelet-derived growth factor (PDGF)-induced Ras activation is required for G1 progression in Chinese hamster embryo fibroblasts (IIC9 cells). Ras stimulates both extracellular signal-related kinase (ERK) activation and RhoA activation in response to PDGF stimulation. Inhibition of either of these Ras-stimulated pathways results in growth arrest. We have shown previously that Ras-stimulated ERK activation is essential for the induction and continued G1 expression of cyclin D1. In this study we examine the role of Ras-induced RhoA activity in G1 progression. Unstimulated IIC9 cells expressed high levels of the G1 cyclin-dependent kinase inhibitor **p27**(KIP1). Stimulation with PDGF resulted in a dramatic decrease in **p27**(KIP1) protein expression. This decrease was attributed to increased **p27**(KIP1) protein degradation. Overexpression of dominant-negative forms of Ras or RhoA completely blocked PDGF-induced **p27**(KIP1) degradation, but only dominant-negative Ras inhibited cyclin D1 protein expression. **C3 transferase** also inhibited PDGF-induced **p27**(KIP1) degradation, thus further implicating RhoA in **p27**(KIP1) regulation. Overexpression of dominant-negative ERK resulted in inhibition of PDGF-induced cyclin D1 expression but had no effect on PDGF-induced **p27**(KIP1) degradation. These data suggest that Ras coordinates the independent regulation of cyclin D1 and **p27** (KIP1) expression by the respective activation of ERK and RhoA and that these pathways converge to determine the activation state of complexes of cyclin D1 and cyclin-dependent kinase in response to mitogen.

L9 ANSWER 8 OF 38 MEDLINE on STN
ACCESSION NUMBER: 97150680 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8995216
TITLE: Geranylgeranylated rho small GTPase(s) are essential for the degradation of p27Kip1 and facilitate the progression from G1 to S phase in growth-stimulated rat FRTL-5 cells.
AUTHOR: Hirai A; Nakamura S; Noguchi Y; Yasuda T; Kitagawa M; Tatsuno I; Oeda T; Tahara K; Terano T; Narumiya S; Kohn L D; Saito Y
CORPORATE SOURCE: Second Department of Internal Medicine, Chiba University Medical School, Inohana-cho, Chuou-ku, Japan.. aizan@med.m.chiba-u.ac.jp
SOURCE: Journal of biological chemistry, (1997 Jan 3) 272 (1) 13-6.

Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20000303
Entered Medline: 19970218

AB Cyclin-dependent kinase (Cdk) enzymes are activated for entry into the S phase of the cell cycle. Elimination of Cdk inhibitor protein p27Kip1 during the G1 to S phase is required for the activation process. An inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase prevents its elimination and leads to G1 arrest. Mevalonate and its metabolite, geranylgeranyl pyrophosphate, but not farnesyl pyrophosphate, restore the inhibitory effect of pravastatin on the degradation of **p27** and allow Cdk2 activation. By the addition of geranylgeranyl pyrophosphate, Rho small GTPase(s) are geranylgeranylated and translocated to membranes during G1/S progression. The restoring effect of geranylgeranyl pyrophosphate is abolished with botulinum **C3 exoenzyme** , which specifically inactivates Rho. These results indicate (i) among mevalonate metabolites, geranylgeranyl pyrophosphate is absolutely required for the elimination of **p27** followed by Cdk2 activation; (ii) geranylgeranylated Rho small GTPase(s) promote the degradation of **p27** during G1/S transition in FRTL-5 cells.

L9 ANSWER 9 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2005:34830 BIOSIS
DOCUMENT NUMBER: PREV200500035526
TITLE: Induction of apoptosis by shikonin through coordinative modulation of the Bcl-2 family, **p27**, and p53, release of cytochrome c, and sequential activation of caspases in human colorectal **carcinoma** cells.
AUTHOR(S): Hsu, Ping-Chi; Huang, Yu-Ting; Tsai, Mei-Ling; Wang, Ying-Jan; Lin, Jen-Kun; Pan, Min-Hsiung [Reprint Author]
CORPORATE SOURCE: Dept Seafood Sci, Natl Kaohsiung Marine Univ, Kaohsiung, Taiwan
mhpan@mail.nkmu.edu.tw
SOURCE: Journal of Agricultural and Food Chemistry, (October 6 2004) Vol. 52, No. 20, pp. 6330-6337. print.
CODEN: JAFCAU. ISSN: 0021-8561.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jan 2005
Last Updated on STN: 19 Jan 2005

AB Shikonin is a main constituent of the roots of Lithospermum erythrorhizon that has antimutagenic activity. However, its other biological activities are not well-known. Shikonin displayed a strong inhibitory effect against human colorectal **carcinoma** COLO 205 cells and human leukemia HL-60 cells, with estimated IC50 values of 3.12 and 5.5 muM, respectively, but were less effective against human colorectal **carcinoma** HT-29 cells, with an estimated IC50 value of 14.8 muM. Induce apoptosis was confirmed in COLO 205 cells by DNA fragmentation and the appearance of a sub-G1 DNA peak, which were preceded by loss of mitochondrial membrane potential, reactive oxygen species (ROS) generation, cytochrome c release,

and subsequent induction of pro-caspase-9 and -3 processing. Cleavages of poly(ADP-ribose) polymerase (PARP) and DNA fragmentation factor (DFF-45) were accompanied by activation of caspase-9 and -3 triggered by shikonin in COLO 205 cells. Here, we found that shikonin-induced apoptotic cell death was accompanied by upregulation of **p27**, p53, and Bad and down-regulation of Bcl-2 and Bcl-XL, while shikonin had little effect on the levels of Bax protein. Taken together, we suggested that shikonin-induced apoptosis is triggered by the release of cytochrome c into cytosol, procaspase-9 processing, activation of caspase-3, degradation of PARP, and DNA fragmentation caused by the caspase-activated deoxyribonuclease through the digestion of DFF-45. The induction of apoptosis by shikonin may provide a pivotal mechanism for its **cancer** chemopreventive action.

L9 ANSWER 10 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:410342 BIOSIS
DOCUMENT NUMBER: PREV200400406877
TITLE: Deacetylase inhibition in malignant melanomas: impact on cell cycle regulation and survival.
AUTHOR(S): Florenes, Vivi Ann [Reprint Author]; Skrede, Martina; Jorgensen, Kjersti; Nesland, Jahn M.
CORPORATE SOURCE: Dept Pathol, Norwegian Radium Hosp, N-0310, Oslo, Norway v.a.florenes@labmed.uio.no
SOURCE: Melanoma Research, (June 2004) Vol. 14, No. 3, pp. 173-181. print.
ISSN: 0960-8931.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Oct 2004
Last Updated on STN: 20 Oct 2004

AB In the present study the deacetylase inhibitor trichostatin A (TSA) was used to elucidate the effect of protein acetylation on cell cycle progression and survival in seven human malignant melanoma cell lines. It was shown that TSA treatment led to a transient G2/M phase delay and accumulation of unphosphorylated retinoblastoma protein (pRB) in all cases. TSA significantly induced protein expression of the cycl in-dependent kinase inhibitor p21WAF1/CIP1 in a dose-dependent manner in all cell lines including those not expressing p21WAF1/CIP1 constitutively, whereas the levels of both wild-type and mutated p53 protein were reduced. The effect on p53 was not a direct result of inhibition of extracellular signal-regulated kinase-1/2 (ERK1/2) activation by TSA, as treatment of the cells with the mitogen-activated protein kinase/extracellular signal-regulated kinase kinase-1 (MEK1) inhibitor PD98059 did not result in decreased p53 protein level. Furthermore, TSA treatment led to reduction in cyclin D1 whereas cyclin D3 accumulated, the latter due to increased protein stability. Similarly, cyclin A protein was reduced whereas cyclin E level was elevated. The effect on p27Kip1, CDK4 and CDK2 was only marginal. In all the examined cell lines, TSA treatment resulted in a profound induction of apoptosis and cleavage of poly-(ADP-ribose)-polymerase (PARP) indicative of caspase activity. Similarly, TSA-mediated apoptosis was reversed by the caspase-inhibitor z-vad-fmk. Altogether, these results suggest that p21WAF1/CIP1 in melanomas is silenced by deacetylation, and furthermore that inhibition of deacetylation may have potential in anticancer therapy of melanoma patients.

L9 ANSWER 11 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:182196 BIOSIS
DOCUMENT NUMBER: PREV200400186114
TITLE: Evidence that receptor activator of nuclear factor (NF)-kappaB ligand can suppress cell proliferation and induce apoptosis through activation of a NF-kappaB-independent and TRAF6-dependent mechanism.
AUTHOR(S): Bharti, Alok C.; Takada, Yasunari; Shishodia, Shishir; Aggarwal, Bharat B. [Reprint Author]
CORPORATE SOURCE: Cytokine Research Section. Dept. of Bioimmunotherapy, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 143, Houston, TX, 77030, USA aggarwal@mdanderson.org
SOURCE: Journal of Biological Chemistry, (February 13 2004) Vol. 279, No. 7, pp. 6065-6076. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Apr 2004
Last Updated on STN: 7 Apr 2004

AB The receptor activator of NF-kappaB ligand (RANKL), a recently identified member of the **tumor** necrosis factor (TNF) superfamily, has been shown to induce osteoclastogenesis and dendritic cell survival. Most members of the TNF superfamily suppress cell proliferation and induce apoptosis, but whether RANKL does so is not known. We demonstrate that treatment of monocyte RAW 264.7 cells with RANKL induces dose-dependent growth inhibition (IC50 = 10 ng/ml) as determined by dye uptake and (3H)thymidine incorporation methods. Suppression of RANKL-induced NF-kappaB activation by dominant-negative IkappaBalpha or by the NEMO-peptide had no effect on RANKL-induced cell growth inhibition. Inhibition of RANKL-induced JNK activation, however, abolished the RANKL-induced apoptosis. Suppression of interaction of RANK with TRAF6 by TRAF6-binding peptide abrogated the anti-proliferative effects of RANKL, suggesting the critical role of TRAF6. Flow cytometric analysis of cells treated with RANKL showed accumulation of cells in G0/G1 phase of the cell cycle, and this accumulation correlated with a decline in the levels of cyclin D1, cyclin D3, and cyclin E and an increase in cyclin-dependent kinase inhibitor **p27** (Kip). Flow cytometric analysis showed the presence of annexin V-positive cells in cultures treated with RANKL. RANKL-induced apoptosis was further confirmed using calcein AM/ethidium homodimer-1 dye and cleavage of poly(ADP-ribose) polymerase (PARP), procaspase 3, and procaspase 9; benzyloxycarbonyl-VAD, the pancaspase inhibitor, suppressed the PARP cleavage. Thus, overall, our studies indicate that RANKL can inhibit cell proliferation and induce apoptosis through a TRAF-6-dependent but NF-kappaB-independent mechanism.

L9 ANSWER 12 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:346211 BIOSIS
DOCUMENT NUMBER: PREV200300346211
TITLE: The histone deacetylase inhibitor MS-275 promotes differentiation or apoptosis in human leukemia cells through a process regulated by generation of reactive oxygen species and induction of p21CIP1/WAF1.

AUTHOR(S): Rosato, Roberto R.; Almenara, Jorge A.; Grant, Steven [Reprint Author]
CORPORATE SOURCE: Medical College of Virginia, Virginia Commonwealth University, MCV Station Box 230, Richmond, VA, 23298, USA stgrant@hsc.vcu.edu
SOURCE: Cancer Research, (July 1 2003) Vol. 63, No. 13, pp. 3637-3645. print.
ISSN: 0008-5472 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jul 2003
Last Updated on STN: 18 Sep 2003

AB Effects of the histone deacetylase (HDAC) inhibitor MS-275 have been examined in human leukemia and lymphoma cells (U937, HL-60, K562, and Jurkat) as well as in primary acute myelogenous leukemia blasts in relation to differentiation and apoptosis. MS-275 displayed dose-dependent effects in each of the cell lines. When administered at a low concentration (e.g., 1 muM), MS-275 exhibited potent antiproliferative activity, inducing p21CIP1/WAF1-mediated growth arrest and expression of differentiation markers (CD11b) in U937 cells. These events were accompanied by an increase in hypophosphorylated retinoblastoma protein and down-regulation of cell cycle-related proteins including cylin D1. However, at higher concentrations (e.g., 5 muM), MS-275 potently induced cell death, triggering apoptosis in apprx70% of cells at 48 h. In contrast to other HDAC inhibitors such as apicidin, the extrinsic, receptor-mediated pathway played a minimal role in MS-275 lethality. However, MS-275 potently induced a very early (e.g., within 2 h) increase in reactive oxygen species (ROS), followed by the loss of mitochondrial membrane potential (DELTApsim) and cytosolic release of cytochrome c. These events culminated in activation of the caspase cascade, manifested by poly(ADP-ribose) polymerase, p21CIP1/WAF1, p27KIP, Bcl-2, and retinoblastoma protein degradation. MS-275 exposure also resulted in diminished expression of cyclin D1 and the antiapoptotic proteins Mcl-1 and XIAP. Administration of the free radical scavenger L-N-acetylcysteine blocked MS-275-mediated mitochondrial injury and apoptosis, suggesting a primary role for ROS generation in MS-275-associated lethality. Lastly, U937 cells stably expressing a p21CIP1/WAF1 antisense construct were significantly more sensitive to MS-275-mediated apoptosis than controls, but they were impaired in their differentiation response. Together, these findings demonstrate that MS-275 exerts dose-dependent effects in human leukemia cells, i.e., p21CIP1/WAF1-dependent growth arrest and differentiation at low drug concentrations and a marked induction of ROS, mitochondrial damage, caspase activation, and apoptosis at higher concentrations.

L9 ANSWER 13 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:318584 BIOSIS
DOCUMENT NUMBER: PREV200300318584
TITLE: Efficacy of Vitamin D compounds to modulate estrogen receptor negative breast **cancer** growth and invasions.
AUTHOR(S): Flanagan, Louise; Packman, Kathryn; Juba, Brian; O'Neill, Sharon; Tenniswood, Martin; Welsh, JoEllen [Reprint Author]
CORPORATE SOURCE: Department of Biological Sciences, University of Notre Dame, 126 Galvin Life Sciences Building, Notre Dame, IN,

46556, USA
joellen.j.welsh.19@nd.edu
SOURCE: Journal of Steroid Biochemistry and Molecular Biology, (February 2003) Vol. 84, No. 2-3, pp. 181-192. print.
CODEN: JSBBEZ. ISSN: 0960-0760.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jul 2003
Last Updated on STN: 9 Jul 2003

AB In estrogen receptor (ER) positive breast **cancer** cells such as MCF-7 cells, the anti-**tumor** effects of 1,25(OH)2D3 (1,25D3) may be secondary to disruption of estrogen mediated survival signals. If so, then sensitivity to 1,25D3 mediated growth arrest could be reduced in estrogen independent breast **cancer** cells. The aim of these studies was to determine the effects of 1,25D3 and EB 1089 on the ER negative, invasive human breast **cancer** cell line SUM-159PT. 1,25D3 and EB1089 reduced SUM-159PT cell growth subsequent to elevation of **p27** and p21 levels. 1,25D3 mediated apoptosis of SUM-159PT cells was associated with an enrichment of membrane bound bax, a redistribution of cytochome c from the mitochondria to the cytosol and PARP cleavage. 1,25D3 and EB1089 also inhibited SUM-159PT cell invasion through an 8 muM Matrigel membrane. In pre-clinical studies, EB1089 dramatically reduced the growth of SUM-159PT xenografts in nude mice. The decreased size of **tumors** from EB1089 treated mice was associated with decreased proliferation and increased DNA fragmentation. Our data support the concept that Vitamin D3 compounds trigger apoptosis by mechanisms independent of estrogen signaling. These studies indicate that Vitamin D3 based therapeutics may be beneficial, alone or in conjunction with other agents, for the treatment of estrogen independent breast **cancer**.

L9 ANSWER 14 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004392851 EMBASE
TITLE: Silibinin causes cell cycle arrest and apoptosis in human bladder transitional cell **carcinoma** cells by regulating CDKI-CDK-cyclin cascade, and caspase 3 and PARP cleavages.
AUTHOR: Tyagi A.; Agarwal C.; Harrison G.; Michael Glode L.; Agarwal R.
CORPORATE SOURCE: R. Agarwal, Dept. of Pharmaceutical Sciences, School of Pharmacy, Univ. of Colorado Health Sci. Center, Denver, CO 80262, United States. rajesh.agarwal@uchsc.edu
SOURCE: Carcinogenesis, (2004) 25/9 (1711-1720).
Refs: 40
ISSN: 0143-3334 CODEN: CRNGDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Bladder **cancer** is the fourth and eighth most common **cancer** in men and women in the USA, respectively. Flavonoid

phytochemicals are being studied for both prevention and therapy of various human malignancies including bladder **cancer**. One such naturally occurring flavonoid is silibinin isolated from milk thistle. Here, we assessed the effect of silibinin on human bladder transitional cell **carcinoma** (TCC) cell growth, cell cycle modulation and apoptosis induction, and associated molecular alterations, employing two different cell lines representing high-grade invasive **tumor** (TCC-SUP) and high-grade TCC (T-24) human bladder **cancer**. Silibinin treatment of these cells resulted in a significant dose- and time-dependent growth inhibition together with a G(1) arrest only at lower doses in TCC-SUP cells but at both lower and higher doses in T-24 cells; higher silibinin dose showed a G(2)/M arrest in TCC-SUP cells. In other studies, silibinin treatment strongly induced the expression of Cip1/p21 and Kip1/**p27**, but resulted in a decrease in cyclin-dependent kinases (CDKs) and cyclins involved in G(1) progression. Silibinin treatment also showed an increased interaction between cyclin-dependent kinase inhibitors (CDKIs)-CDKs and a decreased CDK kinase activity. Further, the G(2)/M arrest by silibinin in TCC-SUP cells was associated with a decrease in pCdc25c (Ser216), Cdc25c, pCdc2 (Tyr15), Cdc2 and cyclin B1 protein levels. In additional studies, silibinin showed a dose- and a time-dependent apoptotic death only in TCC-SUP cells that was associated with cleaved forms of caspase 3 and poly(ADP-ribose) polymerase. Together, these results suggest that silibinin modulates CDKI-CDK-cyclin cascade and activates caspase 3 causing growth inhibition and apoptotic death of human TCC cells, providing a strong rationale for future studies evaluating preventive and/or intervention strategies for silibinin in bladder **cancer** pre-clinical models. .COPYRGT. Oxford University Press 2004; all rights reserved.

L9 ANSWER 15 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004357167 EMBASE
TITLE: A concentrated aglycone isoflavone preparation (GCP) that demonstrates potent anti-prostate **cancer** activity in vitro and in vivo.
AUTHOR: Bemis D.L.; Capodice J.L.; Desai M.; Buityan R.; Katz A.E.
CORPORATE SOURCE: A.E. Katz, Department of Urology, College of Physicians and Surgeons, Columbia University Medical Center, 161 Fort Washington Avenue, New York, NY 10032, United States. aek4@columbia.edu
SOURCE: Clinical Cancer Research, (1 Aug 2004) 10/15 (5282-5292). Refs: 47
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose: Isoflavones have anticancer activities, but naturally occurring isoflavones are predominantly glycosylated and poorly absorbed. Genistein combined polysaccharide (GCP; Amino Up Chemical Co., Sapporo, Japan), is a fermentation product of soy extract and basidiomycetes mycillae that is enriched in biologically active aglycone isoflavones. This study analyzes GCP in vitro and in vivo for potential utility as a prostate

cancer chemopreventative agent. Experimental Design: Androgen-sensitive LNCaP and androgen-independent PC-3 cells were grown with various concentrations of GCP. In vitro cell growth was analyzed by the WST-1 assay, and apoptosis was assessed by fluorescence- activated cell sorting and detection of poly(ADP-ribose) polymerase cleavage using Western blot techniques. Effects of GCP on expression of cell cycle-regulatory proteins p53 (LNCaP only), p21, and **p27** and the protein kinase Akt were considered using Western blot techniques. An in vivo LNCaP xenograft model was used to study the effects of a 2% GCP-supplemented diet on **tumor** growth in comparison with a control diet. Results: GCP significantly suppressed LNCaP and PC-3 cell growth over 72 h (89% and 78% in LNCaP and PC-3, respectively, at 10 μg/ml; $P < 0.0001$). This reduction was associated with apoptosis in LNCaP cells, but not in PC-3 cells. GCP induced **p27** and p53 (LNCaP only) protein expression within 6 h and suppressed phosphorylated Akt in both cell lines. The 2% GCP-supplemented diet significantly slowed LNCaP **tumor** growth, increasing apoptosis ($P < 0.001$), and decreasing proliferation ($P < 0.001$) over 4 weeks. Conclusions: GCP has potent growth-inhibitory effects against prostate **cancer** cell lines in vitro and in vivo. These data suggest GCP has potential as an effective chemopreventive agent against prostate **cancer** cell growth.

L9 ANSWER 16 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004249619 EMBASE
TITLE: Yeast as a model system for anticancer drug discovery.
AUTHOR: Simon J.A.; Bedalov A.
CORPORATE SOURCE: J.A. Simon, Clinical Research Division, Fred Hutchinson Cancer Res. Center, Seattle, WA, United States. jsimon@fhcrc.org
SOURCE: Nature Reviews Cancer, (2004) 4/6 (481-488).
Refs: 59
ISSN: 1474-175X CODEN: NRCAC4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Yeast is widely used as a model organism for investigating many aspects of eukaryotic cell biology. It combines a high level of conservation between its cellular processes and those of mammalian cells with advantages such as simple growth requirements, rapid cell division, ease of genetic manipulation and a wealth of experimental tools for genome-wide analysis of biological functions. How can these advantages be put to use in anticancer drug discovery?

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ACCESSION NUMBER: 2004236930 EMBASE
TITLE: Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor

bortezomib and histone deacetylase inhibitors.
AUTHOR: Pei X.-Y.; Dai Y.; Grant S.
CORPORATE SOURCE: S. Grant, Division of Hematology/Oncology, VA Cmw. Univ./Med. Coll. of Virginia, MCV Station Box 230, Richmond, VA 23298, United States. stgrant@hsc.vcu.edu
SOURCE: Clinical Cancer Research, (1 Jun 2004) 10/11 (3839-3852). Refs: 51
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose: The purpose of this study was to examine interactions between the proteasome inhibitor bortezomib (Velcade) and the histone deacetylase (HDAC) inhibitors sodium butyrate and suberoylanilide hydroxamic acid in human multiple myeloma (MM) cells that are sensitive and resistant to conventional agents. Experimental Design: MM cells were exposed to bortezomib for 6 h before the addition of HDAC inhibitors (total, 26 h), after which reactive oxygen species (ROS), mitochondrial dysfunction, signaling and cell cycle pathways, and apoptosis were monitored. The functional role of ROS generation was assessed using the free radical scavenger N-acetyl-L-cysteine. Results: Preincubation with a subtoxic concentration of bortezomib markedly sensitized U266 and MM.1S cells to sodium butyrate- and suberoylanilide hydroxamic acid-induced mitochondrial dysfunction; caspase 9, 8, and 3 activation; and poly(ADP-ribose) polymerase degradation; resulting in synergistic apoptosis induction. These events were associated with nuclear factor κB inactivation, c-Jun NH(2)-terminal kinase activation, p53 induction, and caspase-dependent cleavage of p21(CIP1), **p27**(KIP1), and Bcl-2, as well as Mcl-1, X-linked inhibitor of apoptosis, and cyclin D1 down-regulation. The bortezomib/HDAC inhibitor regimen markedly induced ROS generation; moreover, apoptosis and c-Jun NH(2)-terminal kinase activation were attenuated by N-acetyl-L-cysteine. Dexamethasone- or doxorubicin-resistant MM cells failed to exhibit cross-resistance to the bortezomib/HDAC inhibitor regimen, nor did exogenous interleukin 6 or insulin-like growth factor I block apoptosis induced by this drug combination. Finally, bortezomib/HDAC inhibitors induced pronounced lethality in primary CD138(+) bone marrow cells from MM patients, but not in the CD138-cell population. Conclusions: Sequential exposure to bortezomib in conjunction with clinically relevant HDAC inhibitors potently induces mitochondrial dysfunction and apoptosis in human MM cells through a ROS-dependent mechanism, suggesting that a strategy combining these agents warrants further investigation in MM.

L9 ANSWER 18 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004059705 EMBASE
TITLE: Molecular Mechanisms for Apigenin-Induced Cell-Cycle Arrest and Apoptosis of Hormone Refractory Human Prostate **Carcinoma** DU145 Cells.
AUTHOR: Shukla S.; Gupta S.
CORPORATE SOURCE: S. Gupta, Department of Urology, James and Eilleen Dicke

Res. Lab., Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, United States
SOURCE: Molecular Carcinogenesis, (2004) 39/2 (114-126).
Refs: 64
ISSN: 0899-1987 CODEN: MOCAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Development of effective agents for treatment of hormone-refractory prostate **cancer** has become a national medical priority. We have reported recently that apigenin (4',5,7-trihydroxyflavone), found in many common fruits and vegetables, has shown remarkable effects in inhibiting cell growth and inducing apoptosis in many human prostate **carcinoma** cells. Here we demonstrate the molecular mechanism of inhibitory action of apigenin on androgen-refractory human prostate **carcinoma** DU145 cells that have mutations in the **tumor** suppressor gene p53 and pRb. Treatment of cells with apigenin resulted in a dose- and time-dependent inhibition of growth, colony formation, and G(1) phase arrest of the cell cycle. This effect was associated with a marked decrease in the protein expression of cyclin D1, D2, and E and their activating partner, cyclin-dependent kinase (cdk)2, 4, and 6, with concomitant upregulation of WAF1/p21, KIP1/**p27**, INK4a/p16, and INK4c/p18. The induction of WAF1/p21 and its growth inhibitory effects by apigenin appears to be independent of p53 and pRb status of these cells. Apigenin treatment also resulted in alteration in Bax/Bcl2 ratio in favor of apoptosis, which was associated with the release of cytochrome c and induction of apoptotic protease-activating factor-1 (Apaf-1). This effect was found to result in a significant increase in cleaved fragments of caspase-9, -3, and poly(ADP-ribose) polymerase (PARP). Further, apigenin treatment resulted in downmodulation of the constitutive expression of nuclear factor-kappaB (NF-κB)/p65 and NF-κB/ p50 in the nuclear fraction that correlated with an increase in the expression of IkappaB-alpha (IκBα) in the cytosol. Taken together, we concluded that molecular mechanisms during apigenin-mediated growth inhibition and induction of apoptosis in DU145 cells was due to (1) modulation in cell-cycle machinery, (2) disruption of mitochondrial function, and (3) NF-κB inhibition. .COPYRGT. 2004 Wiley-Liss, Inc.

L9 ANSWER 19 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003493579 EMBASE
TITLE: Silibinin upregulates the expression of cyclin-dependent kinase inhibitors and causes cell cycle arrest and apoptosis in human colon **carcinoma** HT-29 cells.
AUTHOR: Agarwal C.; Singh R.P.; Dhanalakshmi S.; Tyagi A.K.; Tecklenburg M.; Sclafani R.A.; Agarwal R.
CORPORATE SOURCE: R. Agarwal, Dept. of Pharmaceutical Sciences, School of Pharmacy, Univ. of CO Health Sciences Center, 4200 East Ninth Street, Denver, CO 80262, United States. Rajesh.Agarwal@UCHSC.edu
SOURCE: Oncogene, (13 Nov 2003) 22/51 (8271-8282).

Refs: 51
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Silymarin, a defined mixture of natural flavonoid, has recently been shown to have potent **cancer** chemopreventive efficacy against colon **carcinogenesis** in rat model; however, the mechanism of such efficacy is not elucidated. Here, using pure active agent in silymarin, namely silibinin, we show its antiproliferative and apoptotic effects, and associated molecular alterations in human colon **carcinoma** HT-29 cells. Silibinin treatment of cells at 50-100 μg/ml doses resulted in a moderate to very strong growth inhibition in a dose- and a time-dependent manner, which was largely due to a G0/G1 arrest in cell cycle progression; higher dose and longer treatment time also caused a G2/ M arrest. In mechanistic studies related its effect on cell cycle progression, silibinin treatment resulted in an upregulation of Kip1/**p27** and Cip1/p21 protein as well as mRNA levels, and decreased CDK2, CDK4, cyclin E and cyclin D1 protein levels together with an inhibition in CDK2 and CDK4 kinase activities. In other studies, we observed that G2/M arrest by silibinin was associated with a decrease in cdc25C, cdc2/p34 and cyclin B1 protein levels, as well as cdc2/p34 kinase activity. In the studies assessing biological fate of silibinin-treated cells, silibinin-induced cell cycle arrest and growth inhibition were not associated with cellular differentiation, but caused apoptotic death. The quantitative apoptosis analysis showed up to 15% apoptotic cell death after 48 h of silibinin treatment. Interestingly, silibinin-induced apoptosis in HT-29 cells was independent of caspases activation, as all caspases inhibitor did not reverse silibinin-induced apoptosis. This observation was further confirmed by the findings showing a lack in caspases activity increase and caspases and PARP cleavage as well as a lack in cytochrome c release in cytosol following silibinin treatment of HT-29 cells. Additional studies conducted in mice showed that silibinin doses found effective in HT-29 cells are achievable in plasma, which increases the significance of the present findings and their possible translation in in vivo anticancer efficacy of silibinin against colon **cancer**. Together, these results identify molecular mechanisms of silibinin efficacy as a cell cycle regulator and apoptosis inducer in human colon **carcinoma** HT-29 cells, and justify further studies to investigate potential usefulness of this nontoxic agent in colon **cancer** prevention and intervention.

L9 ANSWER 20 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003157362 EMBASE
TITLE: Inositol hexaphosphate inhibits growth, and induces G1 arrest and apoptotic death of prostate **carcinoma** DU145 cells: Modulation of CDKI-CDK-cyclin and pRb-related protein-E2F complexes.
AUTHOR: Singh R.P.; Agarwal C.; Agarwal R.
CORPORATE SOURCE: R. Agarwal, Department of Pharmaceut. Sciences, School of

Pharmacy, Univ. of Colorado Health Sci. Center, Denver, CO 80262, United States. Rajesh.Agarwal@UCHSC.edu
SOURCE: Carcinogenesis, (1 Mar 2003) 24/3 (555-563).
Refs: 45
ISSN: 0143-3334 CODEN: CRNGDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Cancer** chemopreventive effects of inositol hexaphosphate (IP6), a dietary constituent, have been demonstrated against a variety of experimental **tumors**, however, limited studies have been done against prostate **cancer** (PCA), and molecular mechanisms are not well defined. In the present study, we investigated the growth inhibitory effect and associated mechanisms of IP6 in advanced human PCA cells. Advanced human prostate **carcinoma** DU145 cells were used to study the anticancer effect of IP6. Flow cytometric analysis was performed for cell cycle progression and apoptosis studies. Western immunoblotting, immunoprecipitation and kinase assay were performed to investigate the involvement of G1 cell cycle regulators and their interplay, and end point markers of apoptosis. A significant dose- as well as time-dependent growth inhibition was observed in IP6-treated cells, which was associated with an increase in G1 arrest. IP6 strongly increased the expression of CDKIs (cyclin-dependent kinase inhibitors), Cip1/ p21 and Kip1/**p27**, without any noticeable changes in G1 CDKs and cyclins, except a slight increase in cyclin D2. IP6 inhibited kinase activities associated with CDK2, 4 and 6, and cyclin E and D1. Further studies showed the increased binding of Kip1/**p27** and Cip1/p21 with cyclin D1 and E. In down-stream of CDKI-CDK/cyclin cascade, IP6 increased hypophosphorylated levels of Rb-related proteins, pRb/p107 and pRb2/p130, and moderately decreased E2F4 but increased its binding to both pRb/ p107 and pRb2/p130. At higher doses and longer treatment times, IP6 caused a marked increase in apoptosis, which was accompanied by increased levels of cleaved PARP and active caspase 3. IP6 modulates CDKI-CDK-cyclin complex, and decreases CDK-cyclin kinase activity, possibly leading to hypophosphorylation of Rb-related proteins and an increased sequestration of E2F4. Higher doses of IP6 could induce apoptosis and that might involve caspases activation. These molecular alterations provide an insight into IP6-caused growth inhibition, G1 arrest and apoptotic death of human prostate **carcinoma** DU145 cells.

ACCESSION NUMBER: 2002422237 EMBASE
TITLE: Vitamin D-related therapies in prostate **cancer**.
AUTHOR: Johnson C.S.; Hershberger P.A.; Trump D.L.
CORPORATE SOURCE: C.S. Johnson, Dept. of Pharmacol. and Therapeutics, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, United States. candace.johnson@roswellpark.org
SOURCE: Cancer and Metastasis Reviews, (2002) 21/2 (147-158).
Refs: 113

ISSN: 0167-7659 CODEN: CMRED4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Calcitriol or 1,25-dihydroxycholecalciferol (vitamin D) is classically known for its effects on bone and mineral metabolism. Epidemiological data suggest that low vitamin D levels increase the risk and mortality from prostate **cancer**. Calcitriol is also a potent anti-proliferative agent in a wide variety of malignant cell types including prostate **cancer** cells. In prostate model systems (PC-3, LNCaP, DU145, MLL) calcitriol has significant anti-**tumor** activity in vitro and in vivo. Calcitriol's effects are associated with an increase in cell cycle arrest, apoptosis, differentiation and in the modulation of growth factor receptors. Calcitriol induces a significant G(0)/G(1) arrest and modulates p21(Waf1/Cip1) and **p27**(Kip1), the cyclin dependent kinase inhibitors. Calcitriol induces PARP cleavage, increases the bax/bcl-2 ratio, reduces levels of phosphorylated mitogen-activated protein kinases (P-MAPKs, P-Erk-1/2) and phosphorylated Akt (P-Akt), induces caspase-dependent MEK cleavage and up-regulation of MEKK-1, all potential markers of the apoptotic pathway. Glucocorticoids potentiate the anti-**tumor** effect of calcitriol and decrease calcitriol-induced hypercalcemia. In combination with calcitriol, dexamethasone results in a significant time- and dose-dependent increase in VDR protein and an enhanced apoptotic response as compared to calcitriol alone. Calcitriol can also significantly increase cytotoxic drug-mediated anti-**tumor** efficacy. As a result, phase I and II trials of calcitriol either alone or in combination with the carboplatin, paclitaxel, or dexamethasone have been initiated in patients with androgen-dependent and -independent prostate **cancer** and advanced **cancer**. Patients were evaluated for toxicity, maximum tolerated dose (MTD), schedule effects, and PSA response. Data from these studies indicate that high-dose calcitriol is feasible on an intermittent schedule, the MTD is still being delineated and dexamethasone or paclitaxel appear to ameliorate toxicity. Studies continue to define the MTD of calcitriol which can be safely administered on this intermittent schedule either alone or with other agents and to evaluate the mechanisms of calcitriol effects in prostate **cancer**.

L9 ANSWER 22 OF 38 EMBASE
on STN

ACCESSION NUMBER: 2002418905 EMBASE
TITLE: Polymorphisms in DNA repair and environmental interactions.
AUTHOR: De Boer J.G.
CORPORATE SOURCE: J.G. De Boer, Centre for Biomedical Research, University of Victoria, STC CSC, PO Box 3020, Victoria, BC V8W 3N5, Canada. jdboer@uvic.ca
SOURCE: Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, (30 Nov 2002) 509/1-2 (201-210).
Refs: 79
ISSN: 0027-5107 CODEN: MRFMEC

PUBLISHER IDENT.: S 0027-5107(02)00217-8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The repair of damage to DNA is critical to the survival of a cell. However, not all organisms nor all individuals express a similar response to challenges to their genetic material. Numerous polymorphisms in genes involved in DNA repair have been found in individuals with DNA repair-related disease as well as in the general population. Studies of these variants are critical in understanding the response of the cell to DNA damage. In some cases, these changes predispose the carrier to a greatly increased risk of **cancer**. In other cases, the effects are subtler and depend on interactions between the alleles of several genes, or with environmental factors. Consequently, the health effects of exposure to genotoxic or **carcinogenic** compounds or agents can depend on the variations in these genes. This review will highlight some of the effects that variants, found in many of the genes involved in human DNA repair pathways, have on the response to damage, and their role in susceptibility of the cell and organism to environmental genotoxins. This review will concentrate on the mismatch repair, nucleotide repair, base excision repair, strand break repair, and direct alkyl repair pathways.

L9 ANSWER 23 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002392059 EMBASE
TITLE: Peroxisome proliferator-activated receptor γ ligand troglitazone induces cell cycle arrest and apoptosis of hepatocellular **carcinoma** cell lines.
AUTHOR: Yoshizawa K.; Cioca D.P.; Kawa S.; Tanaka E.; Kiyosawa K.
CORPORATE SOURCE: Dr. K. Yoshizawa, Second Dept. of Internal Medicine, Shinshu Univ. School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. kanamey@hsp.md.shinshuu.ac.jp
SOURCE: Cancer, (15 Nov 2002) 95/10 (2243-2251).
Refs: 33
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB BACKGROUND. Ligand activation of peroxisome proliferator-activated receptor γ (PPARγ) results in the inhibition of proliferation of various **cancer** cells. The aim of this study is to investigate the mechanisms of cell growth inhibition of hepatocellular **carcinoma** (HCC) cell lines by the PPARγ ligand, troglitazone. METHODS. Six HCC cell lines were used to study the effects of troglitazone on cell growth by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay, on cell cycle by flow cytometry, and on the cell cycle-regulating factors of late G1 phase by Western blotting. Apoptosis assays were performed by flow cytometry using

membrane, nuclear, cytoplasmic, and mitochondrial markers. Caspase inhibitors were used to analyze the mechanisms of apoptosis induced by troglitazone. RESULTS. Troglitazone showed a potent dose-dependent effect on the growth inhibition of all six HCC cell lines, which were suppressed to under 50% of control at the concentration of 10 μmol/L. The growth inhibition was linked to the G1 phase cell cycle arrest through the up-expression of the cyclin-dependent kinase inhibitors, p21 and **p27** proteins, and the hypophosphorylation of retinoblastoma protein. Troglitazone induced apoptosis by caspase-dependent (mitchondrial transmembrane potential decrease, cleavage of poly [adenosine diphosphate ribose] polymerase, 7A6 antigen exposure, Bcl-2 decrease, and activation of caspase 3) and caspase-independent (phosphatidylserine externalization) mechanisms. CONCLUSIONS. Our data suggest that ligand activation of PPARγ by troglitazone or modified analogs of the thiazolidinedione class of drugs is a novel target for effective therapy against HCC, because of the significant antiproliferative and programmed cell death induction capabilities demonstrated by troglitazone. .COPYRGT. 2002 American **Cancer** Society.

L9 ANSWER 24 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002352564 EMBASE
TITLE: A pro-apoptotic effect of the CDK inhibitor p57(kip2) on staurosporine-induced apoptosis in HeLa cells.
AUTHOR: Samuelsson M.K.R.; Pazirandeh A.; Okret S.
CORPORATE SOURCE: M.K.R. Samuelsson, Department of Medical Nutrition, Karolinska Institutet, Huddinge University Hospital, Novum, Huddinge SE-141 86, Sweden. magnus.samuelsson@mednut.ki.se
SOURCE: Biochemical and Biophysical Research Communications, (2002) 296/3 (702-709).
Refs: 35
ISSN: 0006-291X CODEN: BBRCA
PUBLISHER IDENT.: S 0006-291X(02)00912-9
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Apoptosis, or programmed cell death, is involved in many biological events, including tumorigenesis. Recently, it has been reported that two members of the Cip/Kip family of CDK inhibitors, p21(Cip1) and **p27** (Kip1), are involved in the regulation of apoptosis. Here, we report that selective expression of the third member in this family, p57(Kip2), potentiated staurosporine-induced apoptosis in HeLa cells. This pro-apoptotic effect was associated with an increased caspase-3 activity. In contrast, glucocorticoid treatment, despite inducing p57(Kip2) expression in HeLa cells, was found to have an inhibitory effect on staurosporine-induced apoptosis. This anti-apoptotic effect of glucocorticoids could be explained by a concomitant increase in Bcl-(xL) expression. The results presented in this study show that p57(Kip2) has a stimulatory effect on apoptosis induced by staurosporine, suggesting a role for p57(Kip2) in the response of **tumor** cells to cytotoxic drugs. .COPYRGT. 2002 Elsevier Science (USA). All rights reserved.

L9 ANSWER 25 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002309464 EMBASE
TITLE: Galectin-3 phosphorylation is required for its anti-apoptotic function and cell cycle arrest.
AUTHOR: Yoshii T.; Fukumori T.; Honjo Y.; Inohara H.; Kim H.-R.C.; Raz A.
CORPORATE SOURCE: A. Raz, Karmanos Cancer Institute, 110 E. Warren Ave., Detroit, MI 48201, United States. raza@karmanos.org
SOURCE: Journal of Biological Chemistry, (1 Mar 2002) 277/9 (6852-6857).
Refs: 36
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Galectin-3, a β-galactoside-binding protein, is implicated in cell growth, adhesion, differentiation, and **tumor** progression by interactions with its ligands. Recent studies have revealed that galectin-3 suppresses apoptosis and anoikis that contribute to cell survival during **metastatic** cascades. Previously, it has been shown that human galectin-3 undergoes post-translational signaling modification of Ser(6) phosphorylation that acts as an "on/off" switch for its sugar-binding capability. We questioned whether galectin-3 phosphorylation is required for its anti-apoptotic function. Serine to alanine (S6A) and serine to glutamic acid (S6E) mutations were produced at the casein kinase I phosphorylation site in galectin-3. The cDNAs were transfected into a breast **carcinoma** cell line BT-549 that innately expresses no galectin-3. Metabolic labeling revealed that only wild type galectin-3 undergoes phosphorylation in vivo. Expression of Ser(6) mutants of galectin-3 failed to protect cells from cisplatin-induced cell death and poly(ADP-ribose) polymerase from degradation when compared with wild type galectin-3. The non-phosphorylated galectin-3 mutants failed to protect cells from anoikis with G(1) arrest when cells were cultured in suspension. In response to a loss of cell-substrate interactions, only cells expressing wild type galectin-3 down-regulated cyclin A expression and up-regulated cyclin D(1) and cyclindependent kinase inhibitors, i.e. p21(WAF1/CIP1) and **p27** (KIP1) expression levels. These results demonstrate that galectin-3 phosphorylation regulates its anti-apoptotic signaling activity.

L9 ANSWER 26 OF 38 EMBASE on STN
ACCESSION NUMBER: 2002308398 EMBASE
TITLE: HPV-16 E6/7 immortalization sensitizes human keratinocytes to ultraviolet B by altering the pathway from caspase-8 to caspase-9-dependent apoptosis.
AUTHOR: Simbulan-Rosenthal C.M.; Velena A.; Veldman T.; Schlegel R.; Rosenthal D.S.
CORPORATE SOURCE: D.S. Rosenthal, Dept. of Molecular Biology, Georgetown Univ. School of Medicine, 3900 Reservoir Rd. NW, Washington, DC 20007, United States. rosenthd@georgetown.edu
SOURCE: Journal of Biological Chemistry, (5 Jul 2002) 277/27

(24709-24716).
Refs: 36
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB UVB from solar radiation is both an initiating and promoting agent for skin **cancer**. We have found that primary human keratinocytes undergo an apoptotic response to UVB. To determine whether these responses are altered during the course of immortalization, we examined markers of apoptosis in primary human foreskin keratinocytes (HFK) transduced with either a retroviral vector expressing the E6 and E7 genes of HPV-16 or with empty vector alone (LXSN-HFK). Whereas LXSN-HFK as well as early passage keratinocytes expressing HPV-16 E6 and E7 (p7 E6/7-HFK) were both moderately responsive to UVB irradiation, late passage-immortalized keratinocytes (**p27** E6/7-HFK) were exquisitely sensitive to UVB-induced apoptosis. After exposure to UVB, enhanced annexin V-positivity and internucleosomal DNA fragmentation were observed in **p27** E6/7-HFK compared with either LXSN- or p7 E6/7-HFK. Caspase-3 fluorometric activity assays as well as immunoblot analysis with antibodies to caspase-3 and poly(ADP-ribose) polymerase revealed elevated caspase-3 activity and processing at lower UVB doses in **p27** E6/7-HFK compared with LXSN- or p7 E6/7-HFK. In addition, the caspase inhibitor DEVD-CHO reduced the apoptotic response and increased survival of all three HFK types. Immunoblot analysis revealed that caspase-8 was activated in all three cell types, but caspase-9 was only activated in **p27** E6/7-HFK. Cell cycle analysis further showed that only **p27** E6/7-HFK exhibit G(2)/M accumulation that is enhanced by UVB treatment. This accumulation was associated with a rapid down-regulation of Bcl-2 in these cells. The immortalization process subsequent to the expression of HPV E6 and E7 may therefore determine UVB sensitivity by switching the mode of apoptosis from a caspase-8 to a Bcl-2-caspase-9-mediated pathway of apoptosis.

L9 ANSWER 27 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001388617 EMBASE
TITLE: Indole-3-carbinol (I3C) induced cell growth inhibition, G1 cell cycle arrest and apoptosis in prostate **cancer** cells.
AUTHOR: Chinni S.R.; Li Y.; Upadhyay S.; Koppolu P.K.; Sarkar F.H.
CORPORATE SOURCE: F.H. Sarkar, Department of Pathology, Wayne State Univ. School of Medicine, 9374 Scott Hall, 540 E. Canfield Avenue, Detroit, MI 48201, United States
SOURCE: Oncogene, (24 May 2001) 20/23 (2927-2936).
Refs: 57
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

Searcher : Shears 571-272-2528

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Prostate **cancer** is one of the most common **cancers** in men and it is the second leading cause of **cancer** related death in men in the United States. Recent dietary and epidemiological studies have suggested the benefit of dietary intake of fruits and vegetables in lowering the incidence of prostate **cancer**. A diet rich in fruits and vegetables provides phytochemicals, particularly indole-3-carbinol (I3C), which may be responsible for the prevention of many types of **cancer**, including hormone-related **cancers** such as prostate. Studies to elucidate the role and the molecular mechanism(s) of action of I3C in prostate **cancer**, however, have not been conducted. In the current study, we investigated whether I3C had any effect against prostate **cancer** cells and, if so, attempts were made to identify the potential molecular mechanism(s) by which I3C elicits its biological effects on prostate **cancer** cells. Here we report for the first time that I3C inhibits the growth of PC-3 prostate **cancer** cells. Induction of G1 cell cycle arrest was also observed in PC-3 cells treated with I3C, which may be due to the observed effects of I3C in the up-regulation of p21(wAF1) and **p27**(Kip1) CDK inhibitors, followed by their association with cyclin D1 and E and down-regulation of CDK6 protein kinase levels and activity. The induction of p21(WAF1) appears to be transcriptionally upregulated and independent of the p53 responsive element. In addition, I3C inhibited the hyperpohosphorylation of the Retinoblastoma (Rb) protein in PC-3 cells. Induction of apoptosis was also observed in this cell line when treated with I3C, as measured by DNA laddering and poly (ADP-ribose) polymersae (PARP) cleavage. We also found an up-regulation of Bax, and down-regulation of Bcl-2 in I3C-treated cells. These effects may also be mediated by the down-regulation of NF-κB observed in I3C treated PC-3 cells. From these results, we conclude that I3C inhibits the growth of PC-3 prostate **cancer** cells by inducing G1 cell cycle arrest leading to apoptosis, and regulates the expression of apoptosis-related genes. These findings suggest that I3C may be an effective chemopreventive or therapeutic agent against prostate **cancer**.

L9 ANSWER 28 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001264730 EMBASE
TITLE: The cyclin-dependent kinase inhibitor (CDKI) flavopiridol disrupts phorbol 12-myristate 13-acetate-induced differentiation and CDKI expression while enhancing apoptosis in human myeloid leukemia cells.
AUTHOR: Cartee L.; Wang Z.; Decker R.H.; Chellappan S.P.; Fusaro G.; Hirsch K.G.; Sankala H.M.; Dent P.; Grant S.
CORPORATE SOURCE: S. Grant, Medical College of Virginia, Virginia Commonwealth University, MCV Station Box 230, Richmond, VA 23298, United States
SOURCE: Cancer Research, (15 Mar 2001) 61/6 (2583-2591).
Refs: 63
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
029 Clinical Biochemistry

037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Interactions between the cyclin-dependent kinase inhibitor (CDKI) flavopiridol (FP) and phorbol 12-myristate 13-acetate (PMA) were examined in U937 human leukemia cells in relation to differentiation and apoptosis. Simultaneous, but not sequential, exposure of U937 cells to 100 nM FP and 10 nM PMA significantly increased apoptosis manifested by characteristic morphological features, mitochondrial dysfunction, caspase activation, and poly(ADP-ribose) polymerase cleavage while markedly inhibiting cellular differentiation, as reflected by diminished plastic adherence and CD11b expression. Enhanced apoptosis in U937 cells was associated with an early caspase-independent increase in cytochrome c release and accompanied by a substantial decline in leukemic cell clonogenicity. Moreover, PMA/FP cotreatment significantly increased apoptosis in HL-60 promyelocytic leukemia cells and in U937 cells ectopically expressing the Bcl-2 protein. In U937 cells, coadministration of FP blocked PMA-induced expression and reporter activity of the CDKI p21(WAF1/CIP1) and triggered caspase-mediated cleavage of the CDKI **p27**(KIP1). Coexposure to FP also resulted in a more pronounced and sustained activation of the mitogen-activated protein kinase kinase/extra-cellular signal-regulated protein kinase cascade after PMA treatment, although disruption of this pathway by the mitogen-activated protein kinase kinase 1 inhibitor U0126 did not prevent potentiation of apoptosis. FP accelerated PMA-mediated dephosphorylation of the retinoblastoma protein (pRb), an event followed by pRb cleavage culminating in the complete loss of underphosphorylated pRb (≈M(r) 110,000) by 24 h. Finally, gel shift analysis revealed that coadministration of FP with PMA for 8 h led to diminished E2F/pRb binding compared to the effects of PMA alone. Collectively, these findings indicate that FP modulates the expression/activity of multiple signaling and cell cycle regulatory proteins in PMA-treated leukemia cells and that such alterations are associated with mitochondrial damage and apoptosis rather than maturation. These observations also raise the possibility that combining CDKIs and differentiation-inducing agents may represent a novel antileukemic strategy.

L9 ANSWER 29 OF 38 EMBASE
on STN
ACCESSION NUMBER: 2001171180 EMBASE
TITLE: Histone deacetylase inhibitors promote apoptosis and differential cell cycle arrest in anaplastic thyroid **cancer** cells.
AUTHOR: Greenberg V.L.; Williams J.M.; Cogswell J.P.; Mendenhall M.; Zimmer S.G.
CORPORATE SOURCE: S.G. Zimmer, Department of Immunology, L.P. Markey Cancer Center, University of Kentucky, 800 Rose Street, Lexington, KY 40536, United States. szimm1@pop.uky.edu
SOURCE: Thyroid, (2001) 11/4 (315-325).
Refs: 52
ISSN: 1050-7256 CODEN: THYRER
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

Searcher : Shears 571-272-2528

AB Little information exists concerning the response of anaplastic thyroid **carcinoma** (ATC) cells to histone deacetylase inhibitors (HDAIs). In this study, the cellular response to the histone deacetylase inhibitors, sodium butyrate and trichostatin A, was analyzed in cell lines derived from primary anaplastic thyroid **carcinomas**. HDAIs repress the growth (proliferation) of ATC cell lines, independent of p53 status, through the induction of apoptosis and differential cell cycle arrest (arrested in G(1) and G(2)/M). Apoptosis increases in response to drug treatment and is associated with the appearance of the cleaved form of the caspase substrate, poly-(ADP-ribose) polymerase (PARP). Cell cycle arrest is associated with the reduced expression of cyclins A and B, the increased expression of the cyclin-dependent kinase inhibitors, p21(Cip1/WAF1) and **p27**(Kip1), the reduced phosphorylation of the retinoblastoma protein (pRb), and a reduction in cdk2 and cdk1-associated kinase activities. In ATC cells overexpressing cyclin E, drug treatment failed to replicate these events. These results suggest that growth inhibition of ATC cells by HDAIs is due to the promotion of apoptosis through the activation of the caspase cascade and the induction of cell cycle arrest via a reduction in cdk2- and cdk1-associated kinase activities.

L9 ANSWER 30 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001131768 EMBASE
TITLE: Induction of CDK inhibitors (p21(WAF1) and **p27** (Kip1)) and BAK in the β-lapachone-induced apoptosis of human prostate **cancer** cells.
AUTHOR: Don M.-J.; Chang Y.-H.; Chen K.-K.; Ho L.-K.; Chau Y.-P.
CORPORATE SOURCE: Dr. Y.-P. Chau, Institute of Anatomy and Cell Biol., School of Life Science, National Yang-Ming University, 155, 2nd Sec., Li-Nung Street, Shih-Pai, Taipei, Taiwan 112, Taiwan,Province of China. leonchau@ym.edu.tw
SOURCE: Molecular Pharmacology, (2001) 59/4 (784-794).
Refs: 35
ISSN: 0026-895X CODEN: MOPMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB β-Lapachone, a novel anti- **neoplastic** drug, induces various **cancer** cells to undergo apoptosis. In a previous report, we showed that β-lapachone-induced apoptosis of HL-60 cells is mediated by oxidative stress. However, in the present study, we found that β-lapachone-induced apoptosis of human prostate **cancer** (HPC) cells may be independent of oxidative stress. In contrast to the 10-fold β-lapachone-induced increase in H(2)O(2) production seen in HL-60 cells, only a 2- to 4-fold increase was observed in HPC cells. N-acetyl-L-cysteine (NAC), a thiol antioxidant, inhibited the apoptosis in DU145 cells after 12 h exposure to β-lapachone. Nonetheless, NAC, along with other antioxidants, failed to exert similar effect in HPC cells subjected to β-lapachone treatment for 24 h. Under this premise, we suggest that the oxidative stress may not play a crucial role in

β-lapachone-mediated HPC cell apoptosis. Here we demonstrate that damage to genomic DNA is the trigger for the apoptosis of HPC cells induced by β-lapachone. According to our results, β-lapachone stimulates DNA dependent kinase expression and poly(ADP-ribose) polymerase cleavage in advance of significant morphological changes. β-Lapachone promotes the expression of cyclin-dependent kinase (cdk) inhibitors (p21(WAF1) and **p27**(Kip1)), induces bak expression, and subsequently stimulates the activation of caspase-7 but not of caspase-3 or caspase-8 during the apoptosis of HPC cells. Taken together, these results suggest that the signaling pathway involving the β-lapachone-induced apoptosis of HPC cell may be by DNA damage, induction of cdk inhibitors (p21 and **p27**), and then subsequent stimulation of caspase-7 activation.

L9 ANSWER 31 OF 38 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998001997 EMBASE
TITLE: Promoting apoptosis: A novel activity associated with the cyclin- dependent kinase inhibitor **p27**.
AUTHOR: Katayose Y.; Kim M.; Rakkar A.N.S.; Li Z.; Cowan K.H.; Seth P.
CORPORATE SOURCE: P. Seth, Medical Breast Cancer Section, Medicine Branch, National Cancer Institute, Bethesda, MD 20892, United States. pseth@box-p.nih.gov
SOURCE: Cancer Research, (1997) 57/24 (5441-5445).
Refs: 20
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **p27**(Kip1), a cyclin-dependent kinase inhibitor, is recognized as a negative regulator of the cell cycle. In this paper, we report that overexpression of **p27**(Kip1) triggers apoptosis in several different human **cancer** cell lines. Using a recombinant adenoviral vector that expresses **p27**(Kip1) (Adp27), we found that overexpression of **p27**(Kip1) in MDA-MB-231 breast **cancer** cells induces apoptosis that was seen by a number of different techniques, including flow cytometry and in situ terminal deoxynucleotidyl transferase-mediated nick end labeling, flow cytometric assay for sub-G1 population, and 4',6-diamindino-2-phenylindole staining. Cleavage of poly(ADP-ribose) polymerase and degradation of cyclin B1, events that are known to be associated with apoptosis, were also observed following overexpression of **p27**(Kip1). This is the first report indicating a role for **p27**(Kip1) in induction of apoptosis.

L9 ANSWER 32 OF 38 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-416805 [39] WPIDS
CROSS REFERENCE: 2002-590689 [63]
DOC. NO. CPI: C2003-110312
TITLE: Prevention of migration of a cell e.g. **tumor** cell involves use of a compound increasing intracellular concentration of cyclin-dependent kinase inhibitor **p27** or **C3 exoenzyme** or decreasing intracellular concentration of Rho-kinase.

DERWENT CLASS: B05
INVENTOR(S): MARKS, A R; MARX, S O ,
PATENT ASSIGNEE(S): (MARK-I) MARKS A R; (MARX-I) MARX S O; (UYCO) UNIV COLUMBIA NEW YORK
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003013638	A1	20030116	(200339)*		19
WO 2003106970	A2	20031224	(200402)	EN	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW					
AU 2003243598	A1	20031231	(200451)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003013638	A1 CIP of	US 2001-766944	20010122
		US 2002-172027	20020614
WO 2003106970	A2	WO 2003-US18970	20030612
AU 2003243598	A1	AU 2003-243598	20030612

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003243598	A1 Based on	WO 2003106970

PRIORITY APPLN. INFO: US 2002-172027 20020614; US 2001-766944 20010122

AN 2003-416805 [39] WPIDS
CR 2002-590689 [63]
AB US2003013638 A UPAB: 20040810
NOVELTY - In the prevention (m1) of migration of a cell, a compound (A1), which increases intracellular concentration of cyclin-dependent kinase inhibitor **p27** (a), increases intracellular concentration of **C3 exoenzyme** (b) or decreases intracellular concentration of Rho-kinase (c) is used.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method (m2) of identifying a chemical compound that inhibits cellular migration involving:

(1) contacting the cells or extract from the cells with the chemical compound; and

(2) b1) detecting an increase in the intracellular concentration of (a) or an increase in the intracellular concentration of (b) or a decrease in the intracellular concentration of (c) in the presence of the chemical compound;

(2) a method (m3) of screening several chemical compounds not known to inhibit cellular migration to identify a chemical compound which

inhibits cellular migration involving:

(1) contacting the cells or extract from the cells with the several chemical compounds;

(2) determining an increase in the intracellular concentration of (a) or an increase in the intracellular concentration of (b) or a decrease in the intracellular concentration of (c) in the presence of the several chemical compounds; and

(3) separately determining whether (a) or (b) is increased or (c) is decreased in the presence of each compound included in the several chemical compounds, to identify the compound which inhibits cellular migration; and

(3) a composition comprising compound identified using (m2) or (m3) or its structural and functional homolog or analog, capable of passing through the cell membrane and a carrier.

ACTIVITY - Antiarteriosclerotic; Cardiant; Vasotropic; Cytostatic; Antimetastatic.

MECHANISM OF ACTION - Vascular smooth muscle cell (SMC) migration inhibitor; Cyclin-dependent kinase inhibitor (**p27**). The inhibitor effect of rapamycin and bFGF on the migration of SMCs isolated from wild type (A) and **p27**(-/-) knockout (B) mice were determined. The migration was measured using a 48 well modified Boyden chamber housing a polycarbonate filter with 8 micro m pores as described by Bornfeldt et al., 1994; Poon et al., 1996. In (A), rapamycin treatment for 48 hours demonstrated a significant inhibitory effect on bFGF-induced SMC migration (IC50 of approx. 2 nM). In contrast no significant inhibition of migration by rapamycin was observed in (B) (IC50 of approx. 200 nM), thus representing a 100 fold increased IC50 as compared to (A).

USE - The method is for preventing migration of a cell e.g. smooth muscle cell, a **tumor** cell, vertebrate cell, mammalian cell or human cell; for treating **cardiovascular diseases** e.g. **atherosclerosis**, **arteriopathy** after **heart** transplantation, or **restenosis** after angioplasty or coronary stent placement; for inhibiting **tumor metastasis** (claimed).

ADVANTAGE - The compound increases the endogenous amount of cyclin-dependent kinase inhibitor **p27** and decreases the endogenous amount of Rho-kinase. The method does not involve administration of gene or gene therapy. Rapamycin has potent inhibitory effects on SMC migration in wild type and **p27** (+/-) mice, but not in **p27** (-/-) knockout mice.

Dwg.0/5

L9 ANSWER 33 OF 38 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER:	2002-590689 [63] WPIDS
CROSS REFERENCE:	2003-416805 [39]
DOC. NO. NON-CPI:	N2002-468710
DOC. NO. CPI:	C2002-167143
TITLE:	Preventing migration of a cell involves increasing intracellular cyclin-dependent kinase inhibitor **p27** activity.
DERWENT CLASS:	B04 D16 P31
INVENTOR(S):	MARKS, A R; MARX, S O
PATENT ASSIGNEE(S):	(MARK-I) MARKS A R; (MARX-I) MARX S O; (UYCO) UNIV COLUMBIA NEW YORK
COUNTRY COUNT:	101
PATENT INFORMATION:	

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002056753	A2	20020725	(200263)*	EN	54
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW					
US 2002098998	A1	20020725	(200263)		
EP 1359904	A2	20031112	(200377)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
AU 2002241950	A1	20020730	(200427)		
JP 2004517880	W	20040617	(200440)		87

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002056753	A2	WO 2002-US1961	20020122
US 2002098998	A1	US 2001-766944	20010122
EP 1359904	A2	EP 2002-707550	20020122
		WO 2002-US1961	20020122
AU 2002241950	A1	AU 2002-241950	20020122
JP 2004517880	W	JP 2002-557267	20020122
		WO 2002-US1961	20020122

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1359904	A2	Based on	WO 2002056753
AU 2002241950	A1	Based on	WO 2002056753
JP 2004517880	W	Based on	WO 2002056753

PRIORITY APPLN. INFO: US 2001-766944 20010122

AN 2002-590689 [63] WPIDS

CR 2003-416805 [39]

AB WO 200256753 A UPAB: 20040624

NOVELTY - Preventing migration of a cell (preferably a smooth muscle cell or a **tumor** cell), comprising increasing intracellular cyclin-dependent kinase inhibitor **p27** activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) identifying (M1) a chemical compound (A), comprising:

(a) contacting cells whose migration is inhibited when intracellular cyclin-dependent kinase inhibitor **p27** activity is increased or contacting an extract from the cells with (A); and

(b) detecting an increase in **p27** activity in presence of (A) to identify (A) as a compound which inhibits cellular migration;

(2) screening several (A) (M2) not known to inhibit cellular migration to identify (A), comprising:

(a) contacting cells (preferably vertebrate cells, more preferably mammalian cells, especially human cells) whose migration is inhibited when

intracellular cyclin-dependent kinase inhibitor **p27** activity is increased or contacting an extract from the cells with the several (A);

(b) determining if **p27** activity is increased in the presence of several (A); and

(c) separately determining if **p27** activity is increased in the presence of each (A);

(3) pharmaceutical composition comprising (A) identified using (M1) or (M2) or a novel structural and functional homolog or analog which is capable of passing through a cell membrane and effective to increase intracellular cyclin-dependent kinase inhibitor **p27** activity and a carrier capable of passing through the cell membrane;

(4) making a composition of matter which inhibits cellular migration, comprising identifying (A) by (M1) or (M2) and synthesizing (A) or a new structural and functional analog or homolog.

ACTIVITY - Cardiant; Antiarteriosclerotic; Vasotropic; Cytostatic; Antitumor; Cardiovascular-Gen.

No biological data is given.

MECHANISM OF ACTION - **p27** activity kinase inhibitor.

USE - For treating **cardiovascular disease** including **atherosclerosis, arteriopathy** after **heart** transplantation or **restenosis** after angioplasty or coronary stent placement, inhibiting **tumor metastasis**, for preparation of a composition for treating an abnormality including **cardiovascular disease** or a **tumor metastasis** (claimed).

ADVANTAGE - (A) when administered to a subject suffering from a disease against which (A) is effective causes reduction, remission or regression of the disease.

Dwg.0/5

L9 ANSWER 34 OF 38 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 97:553239 SCISEARCH
THE GENUINE ARTICLE: XL321
TITLE: Inhibition of smooth muscle cell migration by the p21 cyclin-dependent kinase inhibitor (Cip1)
AUTHOR: Fukui R (Reprint); Shibata N; Kohbayashi E; Amakawa M; Furutama D; Hoshiga M; Negoro N; Nakakouji T; Ii M; Ishihara T; Ohsawa N
CORPORATE SOURCE: OSAKA MED COLL, DEPT INTERNAL MED 1, 2-7 DAIGAKU CHO, TAKATSUKI, OSAKA 569, JAPAN (Reprint); KAKEN PHARMACEUT CO LTD, YAMASHIMA KU, KYOTO 607, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: ATHEROSCLEROSIS, (11 JUL 1997) Vol. 132, No. 1, pp. 53-59. Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND.
ISSN: 0021-9150.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In vascular smooth muscle cells (SMCs), proliferation and migration contribute to lesion formation after arterial injury. In the cell cycle, several cyclin-dependent kinases (cdks) inhibitors are implicated in the

regulating of cyclin-cdk activity such as p21(Cip1), p16(Ink4) and **p27**(Kip1). Although Cip1 inhibits SMC proliferation, its effects on SMC migration are unknown. To test the hypothesis that Cip1 inhibits SMCs migration and proliferation, we transfected the Cip1 gene into a strain of rabbit aortic SMCs (SM3 cells). Both the spreading and the attachment of Cip1-transfected SM3 cells to extracellular matrices (ECMs) were inhibited compared to that of vector-transfected cells. In the modified Boyden's chamber assay the effect of fibronectin on the migratory activity of Cip1-transfected SM3 cells was significantly less than that of vector transfected cells in response to PDGF-BB. These data suggested that Cip1 inhibited both the migration and proliferation of SMC. (C) 1997 Elsevier Science Ireland Ltd.

L9 ANSWER 35 OF 38 CANCERLIT on STN
ACCESSION NUMBER: 2002185257 CANCERLIT
DOCUMENT NUMBER: 22213998 PubMed ID: 12226753
TITLE: E2F activity is essential for survival of Myc-overexpressing human **cancer** cells.
AUTHOR: Santoni-Rugiu Eric; Duro Dominique; Farkas Thomas; Mathiasen Ida S; Jaattela Marja; Bartek Jiri; Lukas Jiri
CORPORATE SOURCE: Department of Cell Cycle and Cancer, Institute of Cancer Biology, Danish Cancer Society, 2100 Copenhagen E., Denmark.. bartek@biobase.dk
SOURCE: ONCOGENE, (2002 Sep 19) 21 (42) 6498-509. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2002466748
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20021018
Last Updated on STN: 20021018

AB Effective cell cycle completion requires both Myc and E2F activities. However, whether these two activities interact to regulate cell survival remains to be tested. Here we have analysed survival of inducible c-Myc-overexpressing cell lines derived from U2OS human osteosarcoma cells, which carry wild-type pRb and p53 and are deficient for p16 and ARF expression. Induced U2OS-Myc cells neither underwent apoptosis spontaneously nor upon reconstitution of the ARF-p53 axis and/or serum-starvation. However, they died massively when concomitantly exposed to inhibitors of E2F activity, including a constitutively active pRb (RbDeltacdk) mutant, p16, a stable **p27** (p27T187A) mutant, a dominant-negative (dn) CDK2, or dnDP-1. Similar apoptotic effect was observed upon down-modulation of endogenous E2Fs through overexpression of E2F binding site oligonucleotides in U2OS-Myc cells, upon expression of RbDeltacdk or dnDP-1 in the Myc-amplified HL-60 (ARF-; p53-) human leukemia cells, and upon co-transfection of Myc and RbDeltacdk in SAOS-2 (ARF+; p53-) human osteosarcoma cells but not in human primary fibroblasts. Consistent with these results, a dnp53 mutant did not abrogate the Myc-induced apoptotic phenotype, which instead strictly depended on caspase-3-like proteases and on Myc transcriptional activity. Our data indicate that in contrast to normal cells, Myc-overexpressing human **cancer** cells need E2F activity for their survival, regardless of their ARF and p53 status, a notion that may have important implications for antineoplastic treatment strategies.

L9 ANSWER 36 OF 38 CANCERLIT on STN
ACCESSION NUMBER: 2002184037 CANCERLIT
DOCUMENT NUMBER: 22198250 PubMed ID: 12209973
TITLE: Monensin-mediated growth inhibition in acute myelogenous leukemia cells via cell cycle arrest and apoptosis.
AUTHOR: Park Woo H; Lee Myung S; Park Keunchil; Kim Eun S; Kim Byoung K; Lee Young Y
CORPORATE SOURCE: Cancer Research Institute, Seoul National University College of Medicine, Korea.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2002 Sep 20) 101 (3) 235-42.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2002458625
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20021018
Last Updated on STN: 20021018

AB Monensin, an Na(+) ionophore, regulates many cellular functions including apoptosis. However, there has been no report about the antitumoral effect of monensin on acute myelogenous leukemia (AML). Here, we investigated the antiproliferative effect of monensin on AML cells in vitro and in vivo. Monensin efficiently inhibited the proliferation of all of 10 AML cell lines, with IC(50) of about 0.5 microM. DNA flow cytometric analysis indicated that monensin induced a G(1) and/or a G(2)-M phase arrest in these cell lines. To address the mechanism of the antiproliferative effect of monensin, we examined the effect of monensin on cell cycle-related proteins in HL-60 cells. The levels of CDK6, cyclin D1 and cyclin A were decreased. In addition, monensin not only increased the **p27** level but also enhanced its binding with CDK2. Furthermore, the activities of CDK2- and CDK6-associated kinases reduced by monensin were associated with hypophosphorylation of Rb protein. Monensin also induced apoptosis in AML cells including HL-60 cells. The apoptotic process of HL-60 cells was associated with changes in Bax, caspase-3, caspase-8 and mitochondria transmembrane potential (Deltapsi(m)). In particular, monensin (i.p. at a dose of 8 mg/kg thrice weekly) significantly reduced the **tumor** size of BALB/c mice that were inoculated s.c. with its derived cell line, WEHI-3BD cells (69% growth inhibition relative to control group; $p < 0.05$). **Tumors** from monensin-treated mice exhibited increased apoptosis, and these **tumor** were immunohistochemically more stained with Bax, Fas and p53 antibodies than control **tumors**. In conclusion, this is the first report that monensin potently inhibits the proliferation of AML cells.

L9 ANSWER 37 OF 38 CANCERLIT on STN
ACCESSION NUMBER: 2002073741 CANCERLIT
DOCUMENT NUMBER: 21397963 PubMed ID: 11507068
TITLE: An adenovirus expressing mutant **p27** showed more potent antitumor effects than adenovirus-**p27** wild type.
AUTHOR: Park K H; Seol J Y; Kim T Y; Yoo C G; Kim Y W; Han S K; Shim Y S; Lee C T

CORPORATE SOURCE: Department of Internal Medicine, Seoul National University College of Medicine, Lung Institute of Medical Research Center, Seoul National University, Seoul 110-744, Korea.
SOURCE: CANCER RESEARCH, (2001 Aug 15) 61 (16) 6163-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2001471454
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20020726
Last Updated on STN: 20020726

AB The main inhibitory action of **p27**, a cyclin-dependent kinase inhibitor (CDKI), arises from its binding with the cyclin E/cyclin-dependent kinase 2 (Cdk2) complex that results in G(1)-S arrest. Degradation of **p27** is mediated by phosphorylation of Thr-187 of **p27**, which follows ubiquitination. In this study, we generated two adenoviruses expressing wild-type **p27** (ad-p27wt) and mutant **p27** (ad-p27mt), with mutation of Thr-187/Pro-188 (ACGCCC) to Met-187/Ile-188 (ATGATC), which was produced with the belief that mutant **p27** would bind cyclin E/CDK2 more stably and show more potent antitumor effects. Ad-p27wt and ad-p27mt expressed **p27** proteins that were indistinguishable by anti-**p27** antibody. A pulse chase experiment showed that p27mt was more resistant to degradation than p27wt. In human lung **cancer** cell lines, ad-p27mt showed stronger growth inhibition than ad-p27wt. Both types of ad-**p27** induced G(1)-S arrest and apoptosis; however, ad-p27mt induced stronger G(1)-S arrest and apoptosis. Intratumoral injection of ad-p27mt induced partial regression of established **tumors** and inhibited the growth of human lung **cancer** xenografts more strongly than ad-p27wt. From these results, we conclude that ad-p27mt has the potential to become a novel and powerful gene therapy tool.

L9 ANSWER 38 OF 38 CANCERLIT on STN
ACCESSION NUMBER: 1999111984 CANCERLIT
DOCUMENT NUMBER: 99111984 PubMed ID: 9894613
TITLE: Novel dipeptidyl proteasome inhibitors overcome Bcl-2 protective function and selectively accumulate the cyclin-dependent kinase inhibitor **p27** and induce apoptosis in transformed, but not normal, human fibroblasts.
AUTHOR: An B; Goldfarb R H; Siman R; Dou Q P
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh School of Medicine, Pennsylvania, USA.
SOURCE: CELL DEATH AND DIFFERENTIATION, (1998 Dec) 5 (12) 1062-75.
Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 1999111984
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990519
Last Updated on STN: 19990519

AB It has been suggested that overexpression of the Bcl-2 oncoprotein in

human **cancer** cells contributes to their resistance to apoptosis induced by chemotherapy. We report here that a novel dipeptidyl proteasome inhibitor, CEP1612, at low concentrations rapidly induces apoptosis in human Jurkat T cells overexpressing Bcl-2 and also in all human prostate, breast, tongue and brain **tumor** cell lines we have tested to date, without exception. In contrast, etoposide, a standard anticancer drug, fails to kill these cells when employed under the same conditions. The apoptosis-inducing abilities of CEP1612 and its analogous compounds match precisely their order for inhibition of the proteasome chymotrypsin-like activity. CEP1612-induced apoptosis is p53-independent, inhibitable by a tetrapeptide caspase inhibitor, and associated with accumulation of the cyclin-dependent kinase inhibitors p21 and **p27** . Furthermore, CEP1612 selectively accumulates **p27** and induces apoptosis in simian virus 40-transformed, but not the parental normal, human fibroblasts. Proteasome inhibitors such as those investigated herein might therefore have potential use as novel anticancer drugs.

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:36:11 ON 23 FEB 2005)

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L10        2479 S "MARKS A"?/AU
L11        2062 S "MARX S"?/AU
L12         197 S L10 AND L11
L13          29 S (L10 OR L11) AND P27
L14          24 S L12 AND P27
L15          29 S L13 OR L14
L16          12 DUP REM L15 (17 DUPLICATES REMOVED)
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- Author(s)

L16 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

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ACCESSION NUMBER:         2003:43009  CAPLUS
DOCUMENT NUMBER:          138:66676
TITLE:                    P27 prevents cellular migration
INVENTOR(S):              Marks, Andrew R.; Marx, Steven O.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U. S.
                          Ser. No. 766,944.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:
```

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003013638	A1	20030116	US 2002-172027	20020614
US 2002098998	A1	20020725	US 2001-766944	20010122
WO 2003106970	A2	20031224	WO 2003-US18970	20030612
WO 2003106970	A3	20040910		

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    W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
       CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
       GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
       LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
       PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
       TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
    RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
       KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
       FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
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BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-766944 A2 20010122
US 2002-172027 A 20020614

AB This invention provides methods of preventing cellular migration and of treating cardiovascular diseases and tumor metastasis by increasing the intracellular concentration of cyclin-dependent kinase inhibitor **p27** or C3 exoenzyme or by decreasing the intracellular concentration of Rho-kinase, and
methods of identifying chemical compds. for use in such treatments.

L16 ANSWER 2 OF 12 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003222365 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12742501
TITLE: Rapamycin: signaling in vascular smooth muscle.
AUTHOR: **Marks A R**
CORPORATE SOURCE: Center for Molecular Cardiology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA.. arm42@columbia.edu
SOURCE: Transplantation proceedings, (2003 May) 35 (3 Suppl) 231S-233S.
Journal code: 0243532. ISSN: 0041-1345.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20030514
Last Updated on STN: 20031218
Entered Medline: 20031217

AB Rapamycin (sirolimus) was initially developed as an antibiotic, then as an immunosuppressant, and recently has been identified as one of the most promising novel agents for prevention of coronary artery stent restenosis. The story of how rapamycin was developed for the prevention of stent restenosis involves the discovery of its antiproliferative and antimigratory actions in vascular smooth muscle and ultimately the demonstration that it inhibits neointimal hyperplasia in a large animal model of restenosis. Rapamycin upregulates the cyclin-dependent kinase inhibitor **p27**(kip1), resulting in cell-cycle arrest at the G1 to S transition. Rapamycin also inhibits other important cellular functions, including protein translation. The precise mechanisms underlying rapamycin's actions have not been fully elucidated. However, its ability to potently inhibit vascular smooth muscle cell migration and proliferation has been the basis for developing rapamycin-eluting coronary artery stents that have reduced in-stent restenosis from about 30% to less than 5% in large clinical trials.

L16 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:556098 CAPLUS
DOCUMENT NUMBER: 137:103877
TITLE: **P27** prevents cellular migration, methods for treatment of cardiovascular diseases and tumor metastases, and compound identification method
INVENTOR(S): **Marks, Andrew R.; Marx, Steven O.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002098998	A1	20020725	US 2001-766944	20010122
CA 2434696	AA	20020725	CA 2002-2434696	20020122
WO 2002056753	A2	20020725	WO 2002-US1961	20020122
WO 2002056753	A3	20030403		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1359904	A2	20031112	EP 2002-707550	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517880	T2	20040617	JP 2002-557267	20020122
US 2003013638	A1	20030116	US 2002-172027	20020614
PRIORITY APPLN. INFO.:			US 2001-766944 A	20010122
			WO 2002-US1961 W	20020122

AB The invention provides methods for preventing cellular migration and for treating cardiovascular diseases and tumor metastasis by increasing cyclin-dependent kinase inhibitor **p27** activity, as well as methods for identifying chemical compds. for use in such treatments.

L16 ANSWER 4 OF 12 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-590689 [63] WPIDS
CROSS REFERENCE: 2003-416805 [39]
DOC. NO. NON-CPI: N2002-468710
DOC. NO. CPI: C2002-167143
TITLE: Preventing migration of a cell involves increasing intracellular cyclin-dependent kinase inhibitor **p27** activity.
DERWENT CLASS: B04 D16 P31
INVENTOR(S): **MARKS, A R; MARX, S O**
PATENT ASSIGNEE(S): (MARK-I) MARKS A R; (MARX-I) MARX S O; (UYCO) UNIV COLUMBIA NEW YORK
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002056753	A2	20020725	(200263)*	EN	54
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT					

RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2002098998 A1 20020725 (200263)
EP 1359904 A2 20031112 (200377) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2002241950 A1 20020730 (200427)
JP 2004517880 W 20040617 (200440) 87

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002056753	A2	WO 2002-US1961	20020122
US 2002098998	A1	US 2001-766944	20010122
EP 1359904	A2	EP 2002-707550	20020122
		WO 2002-US1961	20020122
AU 2002241950	A1	AU 2002-241950	20020122
JP 2004517880	W	JP 2002-557267	20020122
		WO 2002-US1961	20020122

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1359904	A2	Based on	WO 2002056753
AU 2002241950	A1	Based on	WO 2002056753
JP 2004517880	W	Based on	WO 2002056753

PRIORITY APPLN. INFO: US 2001-766944 20010122
AN 2002-590689 [63] WPIDS
CR 2003-416805 [39]
AB WO 200256753 A UPAB: 20040624
NOVELTY - Preventing migration of a cell (preferably a smooth muscle cell or a tumor cell), comprising increasing intracellular cyclin-dependent kinase inhibitor **p27** activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) identifying (M1) a chemical compound (A), comprising:

(a) contacting cells whose migration is inhibited when intracellular cyclin-dependent kinase inhibitor **p27** activity is increased or contacting an extract from the cells with (A); and

(b) detecting an increase in **p27** activity in presence of (A) to identify (A) as a compound which inhibits cellular migration;

(2) screening several (A) (M2) not known to inhibit cellular migration to identify (A), comprising:

(a) contacting cells (preferably vertebrate cells, more preferably mammalian cells, especially human cells) whose migration is inhibited when intracellular cyclin-dependent kinase inhibitor **p27** activity is increased or contacting an extract from the cells with the several (A);

(b) determining if **p27** activity is increased in the presence of several (A); and

(c) separately determining if **p27** activity is increased in the presence of each (A);

(3) pharmaceutical composition comprising (A) identified using (M1) or (M2) or a novel structural and functional homolog or analog which is capable of passing through a cell membrane and effective to increase

intracellular cyclin-dependent kinase inhibitor **p27** activity and a carrier capable of passing through the cell membrane;

(4) making a composition of matter which inhibits cellular migration, comprising identifying (A) by (M1) or (M2) and synthesizing (A) or a new structural and functional analog or homolog.

ACTIVITY - Cardiant; Antiarteriosclerotic; Vasotropic; Cytostatic; Antitumor; Cardiovascular-Gen.

No biological data is given.

MECHANISM OF ACTION - **p27** activity kinase inhibitor.

USE - For treating cardiovascular disease including atherosclerosis, arteriopathy after heart transplantation or restenosis after angioplasty or coronary stent placement, inhibiting tumor metastasis, for preparation of a composition for treating an abnormality including cardiovascular disease or a tumor metastasis (claimed).

ADVANTAGE - (A) when administered to a subject suffering from a disease against which (A) is effective causes reduction, remission or regression of the disease.

Dwg.0/5

L16 ANSWER 5 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2001469194 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11514367
TITLE: Bench to bedside: the development of rapamycin and its application to stent restenosis.
AUTHOR: **Marx S O; Marks A R**
SOURCE: Circulation, (2001 Aug 21) 104 (8) 852-5.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20010917
Entered Medline: 20010913

L16 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2001:538207 CAPLUS
DOCUMENT NUMBER: 135:208778
TITLE: Role for p27Kip1 in vascular smooth muscle cell migration
AUTHOR(S): Sun, Ji; **Marx, Steven O.**; Chen, Hong-Jun; Poon, Michael; **Marks, Andrew R.**; Rabbani, Leroy E.
CORPORATE SOURCE: Cardiology Division, Columbia University College of Physicians and Surgeons, New York, NY, 10032, USA
SOURCE: Circulation (2001), 103(24), 2967-2972
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Rapamycin is a potent inhibitor of smooth muscle cell (SMC) proliferation and migration. Rapamycin-mediated inhibition of SMC proliferation is associated with upregulation of the cyclin-dependent kinase inhibitor p27Kip1. Previously, we showed that mixed embryonic fibroblasts obtained from p27Kip1(-/-) mice were relatively rapamycin-resistant,

suggesting that p27Kip1 plays an integral role in modulating the antiproliferative effects of rapamycin. We hypothesized that the antimigratory effect of rapamycin may also be mediated by p27Kip1. Methods and Results: Rapamycin (1 to 10 nmol/L) inhibited basic fibroblast growth factor-induced migration of wild-type (WT) but not p27Kip1(-/-) SMCs in a dose-dependent manner ($P<0.05$) in a modified Boyden chamber. The effects of rapamycin on aortic SMC explant migration were also studied with WT, **p27**(+/-), and **p27**(-/-) mice. Rapamycin 4 mg kg-1 · d-1 IP for 5 days inhibited SMC migration by 90% in the WT and p27KIP1(+/-) ($P<0.05$) but not P27KIP1(-/-) animals. Conclusions: Lack of p27KIP1 reduces rapamycin-mediated inhibition of SMC migration. These novel findings suggest a role for p27KIP1 in the signaling pathway(s) that regulates SMC migration.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 7 OF 12 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:681144 SCISEARCH
THE GENUINE ARTICLE: 465RB
TITLE: Bench to bedside - The development of rapamycin and its application to stent restenosis
AUTHOR: **Marx S O (Reprint); Marks A R**
CORPORATE SOURCE: Columbia Univ Coll Phys & Surg, Ctr Mol Cardiol, Dept Med, Dept Pharmacol, 630 W 168th St, Box 65, Room 9-401, New York, NY 10032 USA (Reprint); Columbia Univ Coll Phys & Surg, Ctr Mol Cardiol, Dept Med, Dept Pharmacol, New York, NY 10032 USA
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (21 AUG 2001) Vol. 104, No. 8, pp. 852-855. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0009-7322.
DOCUMENT TYPE: Editorial; Journal
LANGUAGE: English
REFERENCE COUNT: 42

L16 ANSWER 8 OF 12 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 1999:975452 SCISEARCH
THE GENUINE ARTICLE: 250YD
TITLE: A role for **P27**(kip1) in smooth muscle cell migration
AUTHOR: Sun J (Reprint); **Marx S O**; Chen H J; **Marks A R**; Rabbani L E
CORPORATE SOURCE: COLUMBIA UNIV, NEW YORK, NY
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (2 NOV 1999) Vol. 100, No. 18, Supp. [S], pp. 3735-3735. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L16 ANSWER 9 OF 12 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999233996 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10217658
TITLE: Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle.
AUTHOR: Gallo R; Padurean A; Jayaraman T; **Marx S**; Roque M; Adelman S; Chesebro J; Fallon J; Fuster V; **Marks A**; Badimon J J
CORPORATE SOURCE: Cardiovascular Biology Research Laboratory, the Zena and Michael Wiener Cardiovascular Institute, Department of Pathology, Mount Sinai School of Medicine, New York, NY, USA.
CONTRACT NUMBER: HL-56180 (NHLBI)
P50-HL-54469 (NHLBI)
RO1-AI-39794 (NIAID)
SOURCE: Circulation, (1999 Apr 27) 99 (16) 2164-70.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20010521
Entered Medline: 19990517

AB BACKGROUND: Although percutaneous transluminal coronary angioplasty (PTCA) is a highly effective procedure to reduce the severity of stenotic coronary atherosclerotic disease, its long-term success is significantly limited by the high rate of restenosis. Several cellular and molecular mechanisms have been implicated in the development of restenosis post-PTCA, including vascular smooth muscle cell (VSMC) activation, migration, and proliferation. Recently, our group demonstrated that rapamycin, an immunosuppressant agent with antiproliferative properties, inhibits both rat and human VSMC proliferation and migration in vitro. In the present study, we investigated (1) whether rapamycin administration could reduce neointimal thickening in a porcine model of restenosis post-PTCA and (2) the mechanism by which rapamycin inhibits VSMCs in vivo. METHODS AND RESULTS: PTCA was performed on a porcine model at a balloon/vessel ratio of 1.7+/-0.2. Coronary arteries were analyzed for neointimal formation 4 weeks after PTCA. Intramuscular administration of rapamycin started 3 days before PTCA at a dose of 0.5 mg/kg and continued for 14 days at a dose of 0.25 mg/kg. Cyclin-dependent kinase inhibitor (CDKI) **p27**(kip1) protein levels and pRb phosphorylation within the vessel wall were determined by immunoblot analysis. PTCA in the control group was associated with the development of significant luminal stenosis 4 weeks after the coronary intervention. Luminal narrowing was a consequence of significant neointimal formation in the injured areas. Rapamycin administration was associated with a significant inhibition in coronary stenosis (63+/-3.4% versus 36+/-4.5%; P<0.001), resulting in a concomitant increase in luminal area (1.74+/-0.1 mm2 versus 3. 3+/-0.4 mm2; P<0.001) after PTCA. Inhibition of proliferation was associated with markedly increased concentrations of the **p27**(kip1) levels and inhibition of pRb phosphorylation within the vessel wall. CONCLUSIONS: Rapamycin administration significantly reduced the arterial proliferative

response after PTCA in the pig by increasing the level of the CDKI **p27**(kip1) and inhibition of the pRb phosphorylation within the vessel wall. Therefore, pharmacological interventions that elevate CDKI in the vessel wall and target cyclin-dependent kinase activity may have a therapeutic role in the treatment of restenosis after angioplasty in humans.

L16 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 1999:415415 BIOSIS
DOCUMENT NUMBER: PREV199900415415
TITLE: Rapamycin inhibits vascular endothelial cell proliferation via induction of a cyclin-dependent kinase inhibitor.
AUTHOR(S): Sun, Ji [Reprint author]; Chen, Hong Jun [Reprint author]; **Marx, Steven O.** [Reprint author]; Schwartz, Allan [Reprint author]; **Marks, Andrew R.** [Reprint author]; Rabbani, LeRoy E. [Reprint author]
CORPORATE SOURCE: Columbia University, New York, NY, USA
SOURCE: Journal of the American College of Cardiology, (Feb., 1999) Vol. 33, No. 2 SUPPL. A, pp. 250A-251A. print.
Meeting Info.: 48th Annual Scientific Session of the American College of Cardiology. New Orleans, Louisiana, USA. March 7-10, 1999. American College of Cardiology.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 1999
Last Updated on STN: 18 Oct 1999

L16 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 1996:708523 CAPLUS
DOCUMENT NUMBER: 126:469
TITLE: Rapamycin resistance tied to defective regulation of p27Kip1
AUTHOR(S): Luo, Yan; **Marx, Steven O.**; Kiyokawa, Hiroaki; Koff, Andrew; Massague, Joan; **Marks, Andrew R.**
CORPORATE SOURCE: Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Molecular and Cellular Biology (1996), 16(12), 6744-6751
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potent antiproliferative activity of the macrolide antibiotic rapamycin is known to involve binding of the drug to its cytosolic receptor, FKBP12, and subsequent interaction with targets of rapamycin, resulting in inhibition of p70 S6 kinase (p70S6K). However, the downstream events that lead to inhibition of cell cycle progression remain to be elucidated. The antiproliferative effects of rapamycin are associated with prevention of mitogen-induced downregulation of the cyclin-dependent kinase inhibitor p27Kip1, suggesting that the latter may play an important

role in the growth pathway targeted by rapamycin. Murine BC3H1 cells, selected for resistance to growth inhibition by rapamycin, exhibited an intact p70S6K pathway but had abnormally low **p27** levels that were no longer responsive to mitogens or rapamycin. Fibroblasts and T lymphocytes from mice with a targeted disruption of the p27Kip1 gene had impaired growth-inhibitory responses to rapamycin. These results suggest that the ability to regulate p27Kip1 levels is important for rapamycin to exert its antiproliferative effects.

L16 ANSWER 12 OF 12 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 91:159183 SCISEARCH
THE GENUINE ARTICLE: FB886
TITLE: CLINICAL AND EPIDEMIOLOGIC ASPECTS OF FELINE IMMUNODEFICIENCY VIRUS AND TOXOPLASMA-GONDII COINFECTIONS IN CATS
AUTHOR: ONEIL S A; LAPPIN M R (Reprint); REIF J S; **MARKS A**; GREENE C E
CORPORATE SOURCE: COLORADO STATE UNIV, COLL VET MED, DEPT CLIN SCI, FT COLLINS, CO, 80523; COLORADO STATE UNIV, COLL VET MED, DEPT MICROBIOL, FT COLLINS, CO, 80523; COLORADO STATE UNIV, COLL VET MED, DEPT SMALL ANIM MED, FT COLLINS, CO, 80523
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF THE AMERICAN ANIMAL HOSPITAL ASSOCIATION, (1991) Vol. 27, No. 2, pp. 211-220.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: AGRI
LANGUAGE: ENGLISH
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Feline immunodeficiency virus (FIV) infection was documented in 57 cats by detecting immunoglobulin G (IgG) antibodies against FIV in serum using an enzyme-linked immunosorbent assay (ELISA). Serum from the majority of cases was assayed for feline leukemia virus (FeLV) **p27** antigen by use of an ELISA, IgG antibodies against coronaviruses using an indirect fluorescent antibody assay, and both immunoglobulin M (IgM) and IgG antibodies against Toxoplasma gondii using ELISA. Serological evidence of coinfection with FeLV, coronaviruses, and T. gondii was shown to be 5.5%, 26.8%, and 57.1% respectively. There was no cat with a coronavirus IgG titer > 1:400 in the study. There was no significant difference between the magnitude of T. gondii-specific IgG titers in cats from this study when compared to healthy cats. Toxoplasma gondii-specific IgM titers were of greater magnitude and were present in serum with or without T. gondii-specific IgG titers more frequently than in healthy cats. Predominant clinical findings included stomatitis, gingivitis, diarrhea, subcutaneous abscessation, anorexia, depression, elevated body temperature, weight loss, and ocular abnormalities. Cats seropositive for T. gondii were more likely to have ocular disease than cats with FIV infection alone. Cats coinfected with FeLV tended to be younger than cats with FIV infection alone, and each of the FeLV-infected cats was clinically ill. A multitude of hematological, biochemical and urinalysis abnormalities were detected; no finding was pathognomonic for FIV infection, and there were no significant differences between cats with FIV infection alone and cats with serological evidence of FIV and T. gondii coinfection. Nine had evidence of clinical feline toxoplasmosis. There

were no major differences in signalment, clinical findings, or laboratory abnormalities of these cats when compared to FIV-naive cats with clinical toxoplasmosis.

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FILE 'HOME' ENTERED AT 14:37:15 ON 23 FEB 2005